

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
CARBARYL

Chemical Code # 000105, DPN # 00169
SB 950 # 142

September 14, 1987

Revised 10/25/88, 3/05/90, 7/31/90, 1/24/92, 9/7/93, 12/20/93, 1/28/98, 3/6/98, 6/28/99, 10/22/99, 9/20/00, 1/7/02, 4/12/02, 7/27/04, 5/25/05 and 3/29/2006

I. DATA GAP STATUS

Chronic rat:	No data gap, possible adverse effects
Chronic dog:	No data gap, no adverse effect
Oncogenicity rat:	No data gap, possible adverse effects
Oncogenicity mouse:	No data gap, possible adverse effects
Reproduction rat:	No data gap, no adverse effect
Teratology rat:	No data gap, no adverse effect
Teratology rabbit ^{c, d} :	No data gap, no adverse effect
Gene mutation ^a :	No data gap, no adverse effect
Chromosome mutation ^a :	No data gap, possible adverse effects
DNA damage ^a :	No data gap, no adverse effect
Neurotoxicity:	Not required at this time ^b

Note, Toxicology one-liners are attached

** indicates acceptable study.

Bold face indicates possible adverse effect.

File name: T060329

Original Toxicology Summary prepared by F. Martz, 9/14/87; revised by J. Gee, 10/88, 3/90, 7/31/90 and 1/24/92. Updated by Kellner, 9/7/93 and 12/20/93. Revised by Gee, 1/28/98, 3/6/98, 6/28/99, 10/22/99, 9/20/00, 1/7/02, 4/12/02, 7/27/04, 5/25/05 and 3/29/06.

^a The data base for genotoxicity on file at DPR may not coincide with that of EPA. Collectively, EPA judged the studies to demonstrate a weakly positive response.

^b There is an acceptable developmental neurotoxicity study on file with no adverse developmental effects reported. There are an acute and a subchronic neurotoxicity study in the rat on file.

^c Data gap previously filled with multiple studies. See T990628.

^d There are two studies with dogs on file that show possible adverse effects.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

RAT CHRONIC

169 - 099 000719 "Chronic Oral Feeding of SEVIN to Rats." (No author, Mellon Institute of Industrial Research, University of Pittsburgh, Report # 21-88, 10/6/58) Sevin, purity not provided, was fed in the diet for 24 months at 0 (ground Purina Laboratory Chow Meal), 0.005 (50), 0.01 (100), 0.02 (200), and 0.04 % (400 ppm) with 20 CFN rats per sex per group. Interim sacrifices were performed at 6 months (four per sex per group at 0, 0.02 (200), and 0.04 % (400 ppm), 9 months (four per sex per group at 0, 0.02 (200), and 0.04 %), and 12 months (six or 8 per sex per group). At the high dose, decreased body weight gain in males, "cloudy swelling" of kidney tubules at 1 year sacrifice, and "cloudy swelling" of central hepatic cords at two years were noted. The changes are equivocal. Chronic NOEL = 200 ppm, NOAEL = \geq 400 ppm. Uncorrectable deficiencies. UNACCEPTABLE and not upgradeable (insufficient numbers at termination, adequacy of high dose not demonstrated, incomplete necropsy and histopathology). (J. Schreider, 5/9/85 and F. Martz, 5/5/87). Re-examined by Green and Gee, 1/24/92.

EPA One-liner: Systemic NOEL = 200 ppm, LEL = 400 ppm (HDT; decreased weight gain in males, kidneys - cloudy swelling of convoluted and loop tubules, liver - cloudy swelling of hepatic cords about central vein). Core grade: minimum for chronic study, supplementary for oncogenicity study.

154, Tab C, Section II, pp 1-3: Rebuttal to #000719 above. Study cannot be upgraded because of uncorrectable deficiencies, i.e., insufficient group size, no feed analysis, no ophthalmoscopic examinations, no evidence of MTD. Based on these considerations, it would be useless to address the rebuttal point by point. No status change. F. Martz, 8/7/87.

157 & 158, 050433 & -34: Supplemental information to #000719 above consisting of copies of laboratory notebooks and pathology records.

Note: The final report from a recently completed combined chronic/oncogenicity study in rats (HWA Study #656-139) has been submitted by Hazleton and has been found to be acceptable by DPR (see -271:126241 under combined rat), thus filling the chronic rodent data gap. A package from the interim sacrifice of this study (-246:112037) and unaudited histopathological findings from the terminal sacrifice (-261:119579) have also been submitted. Kellner, 12/20/93.

DOG CHRONIC

** 169 056429 "One-year Oral Toxicity Study in Beagle Dogs with Carbaryl Technical." (Hazleton (VA), 3/18/87) Technical carbaryl, 99% pure, was fed at 1250, 400, 125, or 0 ppm in the diet (about 34, 11, or 3.6 mg/kg/day) to 6/sex/dose for 1 year. Cholinesterase inhibition >25% at 1250 and 400 ppm, ChE NOEL = 125 ppm; neutrophilia, slightly increased inorganic phosphorus, and decreased serum albumin at 1250 ppm, not regarded to be adverse effects by reviewer, NOEL = 400 ppm; no clinical signs or organ toxicity, no adverse effects, toxicologic NOAEL = 1250 ppm (HDT). COMPLETE and ACCEPTABLE. F. Martz, 5/19/87.

EPA One-liner: No one-liner on file.

169-099 000718 "Chronic Toxicity of SEVIN for Dogs." (Mellon Institute, report #21-89, 10/1/58) Technical carbaryl was given by oral capsule at 7.2, 1.8, 0.45, or 0 mg/kg/day (approximately equivalent to 400, 100, 25, or 0 ppm in the feed), 5 days/week for 1 year to 3-4 Cocker or Basenji hybrids/level. "... Cloudy swelling of the convoluted and loop [kidney] tubules; sudanophilic dust in the glomeruli..." at 7.2 mg/kg, not regarded by lab to be degenerative change, significance questionable. No other effects, major deficiencies, insufficient information. UNACCEPTABLE and not upgradeable. J. Schreider, 5/10/85.

EPA One-liner: Systemic NOEL = 1.8 mg/kg, LEL = 7.2 mg/kg (diffuse cloudy swelling of proximal convoluted tubule). Core grade: supplementary.

154, Tab C, Section III, pp 3-4; Rebuttal to #000718 above, has no useful information on which to upgrade Mellon Institute study #21-89. Moot because repeat study (#056429 above) was accepted. F. Martz, 5/19/87 (no worksheet).

SUBCHRONIC, DOG

169-239 98146 "Subchronic Toxicity Study in Dogs with Carbaryl Technical." (N. N. Hamada, Hazleton Laboratories America, Inc., Vienna, Virginia; Report # HLA 656-152; 8/5/91 [completed 3/28/91]). Carbaryl Technical (99.3%, Lot # 87191); 6 dogs/sex/dose; 0, 20, 45, 125 ppm in the diet. Observations: No mortalities due to test article were observed. No significant changes in bodyweight gain, total food consumption, food utilization, clinical observations, ophthalmic changes, or gross pathological changes considered treatment related were observed at any treatment level. Statistically significant decreases in plasma cholinesterase were seen in the 20, and 125 ppm males during Week 2 but were considered incidental. No significant inhibition of erythrocyte or brain cholinesterase levels were seen. NOEL (M/F) >125 ppm (M: 3.83 mg/kg/day, F: 4.11 mg/kg/day; based on no treatment related effects at high dose treatment); Supplemental (length of treatment, limited parameters measured, no histopathology, dose selection not justified: too low) (Miller, 1/21/98)

COMBINED RAT

** 169 - 271 126241 Hamada, N. "Combined Chronic Toxicity and Oncogenicity Study with Carbaryl Technical in Sprague-Dawley Rats" (Hazleton Washington, Inc. (HWA), HWA Study No. 656-139, 9/7/93). Carbaryl technical (lot #12-CNG-32, purity 99%) was administered in the feed at concentrations of 0, 250, 1500, and 7500 ppm to 90 Sprague-Dawley rats/sex/group (control and high-dose) and 80 rats/sex/group (low- and mid-dose) for 104 weeks. Ten animals/sex/group were sacrificed for clinical pathology evaluation after 26, 52, 78 and 104 weeks; an additional 10/sex (control and 7500 ppm) were sacrificed at week 57 after receiving basal diet from week 53-57 (recovery groups). Body weights and food consumption were significantly lower in high-dose rats during most of the study and in 1500 ppm females at weeks 53 and 105. Cholinesterase (ChE) NOEL = 250 ppm (significant ChE inhibition at the mid- and high dose for erythrocyte and brain ChE and at the high dose for plasma ChE). Nonneoplastic findings: pigment, hyperplasia and eosinophilic foci (liver), foamy macrophages and pneumonitis (lung), vacuolization (pancreas), transitional cell hyperplasia (kidney and urinary bladder), follicular cell hypertrophy (thyroid), nerve degeneration (sciatic nerve/skeletal muscle), decreased leukocytes, unilateral and bilateral cataracts. Systemic (female) NOEL = 250 ppm (male weight effects on occasion at all dose levels). **Possible Adverse Effects:** neoplastic lesions at the high dose level in the urinary bladder (papilloma and carcinoma), kidney (single transitional cell carcinoma in males), liver (adenoma and foci) and thyroid (adenoma and a single carcinoma). ACCEPTABLE. Kellner and Gee, 12/20/93. In the process of

developing a risk characterization document, the effect of carbaryl on male body weight was reexamined. There were 3 occasions when the total body weight of males at 250 ppm was statistically significantly lower than controls, (3%), this is of doubtful toxicological significance. Therefore, the NOEL for this study is considered to be 250 ppm as for females in the initial review. (Gee, 5/25/05)

169-246 112037, "Combined Chronic Toxicity and Oncogenicity Study with Carbaryl Technical in Sprague-Dawley Rats." (52-Week Interim Report with 4-Week Recovery) (N. Nicki Hamada, Hazleton Washington, Inc., Vienna, VA., Report #656-139, 12 December 1991). Sevin Technical (Carbaryl), 99.6% purity was used. This is a 52-week interim report (including a 4-week recovery period) for a 104 week study. The test compound was administered in the diet for 52 weeks at 0 (Purina⁷ Certified Rodent Chow⁷ # 5002), 250, 1500 or 7500 ppm with 80 (low and mid-dose) or 90 (control and high dose) Crl:CD BR rats per sex per group. Ten (10) per sex per group were necropsied at week 53. Additionally, following 52 weeks of treatment, 10 per sex each from the control and high dose groups were designated recovery animals and were placed on the basal diet for 4 weeks. These rats were sacrificed and necropsied at week 57. Reduced body weights were noted throughout the study at 1500 (females, 3% to 7% reduction) and 7500 (both sexes, 15% to 38% reduction) ppm. Increased relative (to terminal body weight) liver and kidney weight ratios were indicated for both sexes at 1500 and 7500 ppm. Hepatocellular intracytoplasmic hyaline inclusions were noted in 1 and 4 high dose males respectively at the unscheduled and interim (week 53) sacrifices. Histopathology of recovery animals (week 57 sacrifice) showed the absence of this finding, suggesting reversibility.

Adverse effects are not indicated. Possible Chronic NOEL = 250 ppm (bodyweight reduction). ChE NOEL = 250 ppm (based on plasma, RBC and brain ChE inhibition at 1500 and 7500 ppm). **Unacceptable**, this 52-week interim report does not satisfy chronic data requirements in the rat for a food-use active ingredient. It is considered supplemental information, pending receipt of the final report. (H. Green, 1/15/92, and Gee, 1/23/92)

Note: Final report has been submitted and is acceptable; see 169 -271:126241.

169-261 119579 [Addendum to -246:112037] Hamada, N. "Chronic Toxicity/ Oncogenicity Study with Carbaryl Technical in Rats Preliminary Data" (HWA Study No. 656-139, 11/3/92). Carbaryl technical was administered in the feed to Sprague-Dawley Rats at 0, 250, 1500 or 7500 ppm; this submission concerns preliminary unaudited neoplastic findings from terminally sacrificed rats and intercurrent deaths from Hazleton study #656-139. **Possible Adverse Effects:** Increased incidence of bladder (males and females), thyroid (males) and hepatocellular (females) neoplasia. Increased sciatic nerve and skeletal muscle degeneration in the high-dose group. Kellner and Gee, 8/31/93.

RAT ONCOGENICITY

Also See Combined Rat.

EPA One-liner: Rat Oncogenicity study on file (Carpenter et al., 1961, J. Agriculture and Food Chemistry, 9:30-39.); Core Supplementary.

MOUSE ONCOGENICITY

**** 267 123769** Hamada, N. "Oncogenicity Study with Carbaryl Technical in CD-1® Mice." (Hazleton Washington, Inc. (HWA), HWA Study No. 656-138, 5/20/93). Carbaryl technical (lot #87191, purity 99.3%) was administered in the feed at concentrations of 0, 100, 1000 and 8000

ppm to 80 CD-1® mice/sex/group for 104 weeks. Ten animals/sex/group were sacrificed at interim (week 52). Non-neoplastic findings included increased incidence of intracytoplasmic (protein-like) droplets in the superficial transitional epithelium of the urinary bladder and increased hematopoiesis and pigment in the spleen (high-dose). High-dose mice appeared unthrifty (hunched, languid, thin, urine stains, rough coat and opaque eyes) and showed reduced body weight (18%) and food consumption (22%). Lung and ovary weight were reduced and liver weight was elevated for the high dose groups. **Systemic NOEL = 100 ppm** (from effects seen in the urinary bladder). Cholinesterase activity (RBC-CHE and BR-CHE) showed significant decreases in the mid- and high-dose groups; **ChE NOEL = 100 ppm. Possible adverse effects:** Increased hemangioma/hemangiosarcoma in all male dose groups and high-dose females; increased renal tubular cell adenoma and carcinoma in high-dose males and hepatocellular adenoma and carcinoma in high-dose females. Unilateral or bilateral posterior lens cataracts at high-dose. ACCEPTABLE. (Kishiyama, Kellner and Gee, 8/23/93).

254 116336 [Addendum to -267:123769] Hamada, N. "Oncogenicity Study with Carbaryl Technical in Mice Preliminary Data." (Hazleton Washington, Inc., HWA Study No. 656-138, 7/21/92). Carbaryl technical, purity 99.3%, was administered in the feed at levels of 100, 1000 and 8000 ppm to 80 CD-1⁷ mice/sex/group for 104 weeks; this submission reports preliminary neoplastic findings from terminally sacrificed mice and intercurrent deaths. **Possible Adverse Effects:** There were increased incidences of renal (high-dose males), hepatocellular (high-dose females), and vascular (males and females) neoplasia. Also reported was increased incidence of unilateral and bilateral cataracts in high-dose male and female mice. Supplemental Data. (Kellner and Gee, 8/6/93.)

169-247 112020 Partial duplicate of -267:123769. Contains data and analysis up to and including the 52-Week interim sacrifice. No worksheet. (Kellner, 9/7/93.)

169 – 400 177757 E. Debruyne "Carbaryl: 52-Week Toxicity Study in the CD1 Mouse Target Organs Cell Cycling Assessment." (Rhone-Poulenc Agro, Study SA 97529, 12/02/98) Paraffin blocks containing tissues were obtained from study HWA 656-138 [Record 123769, Hazleton Labs, 1993]. Female livers and male kidneys of mice from the 8000 ppm treatment group, 10/group, sacrificed after 52 weeks of exposure, were compared with untreated control mice. A section of rat duodenum was used as the positive control for immunohistochemical staining for proliferating cell nuclear antigen (PCNA) to assess cell cycling. Deparaffinized tissue sections were reacted with PCNA, amplified with a secondary antibody, submitted to a complex of streptavidin-peroxydase and reacted with the chromogen aminoethylcarbazol. PCNA-positive cells had red-stained nuclei and non-proliferating nuclei were blue. 1000 cells were evaluated per section of liver and kidney. For male kidneys, PCNA-positive renal cortical tubular cells had a mean of 1.20 ± 1.75 per 1000 cells (range of 0 to 4) while treated tissue had 3.90 ± 2.18 (range of 1 to 7). For female hepatocytes, control mean was 4.60 ± 7.68 (range of 0 to 23) and treated, 8.33 ± 3.84 (range of 2 to 13). The results were interpreted as of uncertain toxicological significance for male kidneys and not significant in female livers, based on the range of variability and the small difference in males and that all treated female values were within control range. Therefore, overall, increased cell cycling of apparent target tissues was not clearly demonstrated by this approach. Positive control data from the rat were not, however, included in the report. Supplemental study with no worksheet. (Gee, 3/28/06)

169 - 099 000717 (with rebuttal and supplemental information in -154 and -161, 050437) "Results of Eighty Weeks of Inclusion of SEVIN in the Diet of Mice." (Mellon Institute, report #26-53, 6/11/63) Technical carbaryl, 99.8% pure, was fed in diet at 400, 100, or 0 ppm to CD-1 mice, 48/sex/level for 80 weeks. There was approx. 50% mortality at 80 weeks, in all groups, 2 of these autolyzed or cannibalized; 12/sex/level sacrificed at 80 weeks with no explanation of

the survivors' fates; latter found only in supplemental information in #050437; no onco effects, but

study generated little useful information. UNACCEPTABLE and not upgradeable J. Schreider, 5/10/85 and F. Martz, 8/7/87)

EPA One-liner: Negative - dietary at 400 ppm (HDT)/day/2 yr. Core grade: supplementary.

169-154, Tab C, Section V, pg. 5: Rebuttal of #000717 above. Study cannot be upgraded. Twelve/sex/level were interim sacrificed at 80 weeks and the study terminated at 2 years. Results of the terminal sacrifice are not given in the report. Approximately 50% of the mice died by 80 weeks, and one-half of these lost to autolysis and/or cannibalism; only 2-10 mice/level examined from interim sacrifice through termination; the tissue inventory is incomplete. Based on these considerations, the study is not upgradeable and the rebuttal will not be discussed further. F. Martz, 8/7/87.

169-161, 050437: Supplemental information to #000717 above, having the following:

Tab A: Copy of laboratory notebook 806. Individually lists by animal number, the calendar date and fate, age at fate, clinical observations, and gross necropsy observations. Note that this provides the first indication that the study actually went beyond 80 weeks. The report stated that 12/sex/level were sacrificed at 80 weeks with no explanation of the survivors' disposition.

Tab B: Copy of laboratory notebook 807. Contains diet room records showing amounts of carbaryl and feed used for each batch of feed mix.

Tab C: Consultant pathologist's second opinion of liver findings. No new effects noted. The slight increase in hepatocellular nuclear polyploidy noted originally at 80 weeks was re-diagnosed as being "...present in the livers of all mice examined...." There was no change in the hepatocellular tumor incidence.

Tab D: Pathology report from 80 week sacrifice through termination.

Tab E: Pathology report from first death through 80 week sacrifice.

F. Martz, 8/7/87.

MOUSE SUBCUTANEOUS ONCOGENICITY

169-023, 038178 (with rebuttal and additional information in -154 and -160, 50436) "Mammalian Toxicity of 1-Naphthyl-N-methylcarbamate (SEVIN Insecticide)." Mellon Institute, in J. Agr. Food Chem., 9:30-39 (1961); technical carbaryl in 0.25% agar by subcutaneous injection once weekly to 3 month old A/J or C3H males, 10 or 0 mg/mouse, 30/level, and 30 untreated controls, for 5 months with gross examination for lung masses at 8 months of age. UNACCEPTABLE, contains no useful information. (J. Schreider, 5/6/85 and F. Martz, 5/5/87)

EPA One-liner: Negative - subcutaneous injection of 5% (10 mg) agar dilution (HDT) once/wk/20 wk. Core grade: supplementary.

169-154, Tab C, Section IV, pg. 5; Rebuttal of #038178 above. Study cannot be upgraded and rebuttal will not be further addressed. No status change. F. Martz, 5/5/87.

169-160, 050436; Copies of 4 laboratory notebook pages for #038178 above.

RAT REPRODUCTION

** 169 - 410 182115 Tyl, R. W., C. B. Myers and M. C. Marr " Two-generation reproductive toxicity evaluation of Carbaryl (RPA007744) administered in the feed to CD®

(Sprague-Dawley) rats." (Research Triangle Institute, RTI 65C-07407-400, 5/24/2001)
Technical grade carbaryl, 99.1%, was fed in the diet at 0, 75, 300 or 1500 ppm to 30/sex/group CD® Sprague Dawley rats for 1 litter per generation, two generations. At 1500 ppm, there were decreased body weight and food consumption in F0 and F1 parental animals with smaller effects at 300 ppm. In offspring, there were lower body weights, delay in vaginal opening and preputial separation (measured in F1 pups only), increased mortality in F1 and F2 pups at 1500 ppm with an increase in mortality in F2 pups at 300 ppm during lactation, especially pnd 0 - 4 (survival index of 98.3% for controls, 92.0% at 300 ppm - not statistically significant, and 88.9% at 1500 ppm - also not significant). Parental systemic NOEL = 75 ppm; reproductive NOEL = 1500 ppm (no effects); pup NOEL = 75 ppm. No specific adverse reproductive effects. ACCEPTABLE. (Gee, 1/7/02).

169 - 388 170645 A Carbaryl reproductive toxicity: Assessment of data adequacy for hazard assessment and evaluation of potential for increased susceptibility to the young.@ (J. P. Rieth, Rhone-Poulenc Ag Company, report no JPR0199, May 20, 1999). The document is an assessment of the results of reproductive and developmental studies in view of FQPA and the need for an additional 10X safety factor and addressed to US EPA. The reproduction studies completed in 1966 and 1972 were discussed and a statement was made that a new reproduction study is in progress and due in December, 2000. SUPPLEMENTAL. (Gee, 9/10/99)

169 - 099 000716 "Results of a Three Generation Reproduction Study on Rats Fed SEVIN in Their Diets." (Mellon Institute report #28-53, 4/20/65) Technical grade carbaryl, 99.8% pure, in the feed at 10, 2.5, or 0 mg/kg/day to 12-20 females/level, males unspecified, ($F_{2a} \rightarrow F_{3b}$ for teratology portion); no reproductive effects, but no MTD; UNACCEPTABLE because of numerous deficiencies. J. Schreider, 5/10/85 and F. Martz, 8/6/87.

EPA One-liner: Reproductive, fetotoxic, and maternal NOEL=10 mg/kg (HDT). Core grade: minimum.

169 - 130 037909; Exact duplicate of #000716 above. F. Martz, 8/7/87.

154, Tab C, Section VI, pages. 6-7, Rebuttal of #000716 above. Basically, an explanation of the study design in comparison to a FIFRA guideline study. My response is to quote the registrant's own rebuttal of the teratology portion of this study given in Section VII: "The value of this study will not be discussed in detail as the dosage levels used...were so much lower than those used in a subsequent study." F. Martz, 8/6/87 (no worksheet).

162, 050438; Additional data included with rebuttal for #000716 above, consisting of photocopies of laboratory notebooks 911, 914, 945, and 951 as well as typed text and tables:

Tab A: Contains the "Diet Room Record" documenting the amounts of carbaryl and feed used for diet preparation;

Tab B: Individual body weights of F_0 , F_{1a} , and F_{1b} , and litter records for the F_0 and F_{1a} rats;

Tab C: Body weights and mating records of the F_2 generation;

Tab D: Litter records for pups of the F_2 females;

Tabs E, F, and G: Pathology summaries and raw data for fetuses, weanlings, and 90 day old individuals from the F_3 offspring.

Additional data can not upgrade study. F. Martz, 5/19/87.

169-099 000712 (with rebuttal and additional data in -154, -165, 050441, and -166, 050442, 050955 & 56). "Comparative Study of Dietary Inclusion versus Stomach Intubation on Three-Generations of Reproduction, on Teratology and on Mutagenesis." (Mellon Institute,

report #35-65, 8/31/72) Technical carbaryl, 99.6% pure, in feed at 200, 100, 25, 7, or 0 mg/kg/day; by gavage in corn oil at 100, 25, 7, 3, or 0 mg/kg/day; in feed containing corn oil at 100 or 0 mg/kg/day; 5 days/week (m->f); limited->complete histopathology on P₀ and F_{3a} at 21 and 90 days old;

FEEDING RESULTS: MATERNAL - reduced weight gain at 200 mg/kg; NOEL = 100 mg/kg maternal, 200 mg/kg repro;

FEEDING/CORN OIL RESULTS: no effects at 100 mg/kg;

GAVAGE RESULTS: MATERNAL - tremors, mortality, and reduced weight gain at 100 mg/kg;

REPRO - decreased litter size at 100 mg/kg; NOEL = 25 mg/kg maternal and repro.

PROBLEMS: excessive postnatal mortality days 4-21 potentially hiding subtle effects, makes otherwise upgradeable study UNACCEPTABLE. J. Schreider, 5/13/85 and F. Martz, 8/7/87.

EPA One-liner for gavage: Reproductive NOEL = 25 mg/kg, fetotoxic LEL = 100 mg/kg (decreased "viable" fetuses), maternal LEL = 100 mg/kg (HDT; decreased weight gain, cholinergic signs, mortality). Core grade: Minimum.

EPA One-liner for feeding: Reproductive and fetotoxic NOEL = 200 mg/kg (HDT), maternal LEL = 200 mg/kg (decreased weight gain). Core grade: minimum.

169 - 130 037913: Exact duplicate of #000712 above.

169 - 154, Tab C, Section X, pages 10-11, Rebuttal of #000712 above. Specific comments are as follows:

- A. Rebuttal: "A single daily dose intubation procedure is not considered by the authors to be a proper model for human exposure to pesticide residues in the diet." This concerns our criticism that carbaryl was administered by feed rather than gavage.

Response: We disagree. Humans may consume a carbaryl-laden meal in 10 minutes, whereas rats nibble their feed continuously albeit mostly with the first several hours of darkness.

- B. Rebuttal: "Furthermore, the previous...studies using dietary inclusion ...demonstrated no reproductive or teratogenic effects."

Response: Dose levels (25 mg/kg HDT) were insufficient.

- C. Rebuttal: "...the purpose of this study was [to compare]...the potential effect on reproduction in rats following daily dietary inclusion or gastric intubation. To attempt to compare the procedure used to the current FIFRA guidelines is inappropriate."

Response: We agree. Were it not for excessive postnatal mortality in particular, the study could be acceptable to fill the data gap.

- D. Rebuttal: "The results of this study were, and are, very significant. Daily gastric intubation of carbaryl resulted in maternal cholinesterase inhibition and mortality, as well as some effect on reproduction but the appropriate potential hazard route of administration, dietary inclusion, was without significant deleterious effect."

Response: We disagree that dietary inclusion is the most appropriate route of administration for reasons stated above.

- E. Comment: The respondent seems to have missed the overwhelming significance of this study: the complete absence of teratogenicity with only minimal fetotoxicity or reproductive toxicity within the parameters covered at a gavage-administered dose level clearly producing significant maternal toxicity. That alone supports the relative "safety" of carbaryl to the developing organism. F. Martz, 8/6/87.

169 - 165, 050441 Additional data submitted with rebuttal for rat reproduction study with teratology and dominant lethal components (Mellon report #35-65, CDFA #169-099, #000712 and 027204), consisting of photocopies of laboratory notebooks;

Tab A: Individual body weights of F₀ rats and identification of male-female mating pairs for F_{1a}, F_{1b}, and F_{1c} offspring;

Tab B: "Diet Room Record" documenting usage of carbaryl and feed for diet preparation from start to 8/9/71, continued in Tab J;

Tab C: Individual body weights of oral gavage F_0 parents and F_{1a} offspring from weaning through gestation of F_{2a} , and clinical observations.

Tab D: Contains body weight data for what appears to be a 4 week pilot study otherwise unidentified;

Tab E: Litter records for F_0 matings;

Tab F: Individual body weights and mating-pair records for feed-treated F_{1a} ;

Tab G: Contains F_{1a} body weight information continued from Tab C, and F_{2a} body weights;

Tab H: Litter records for F_{1a} matings;

Tab I: Body weight records for F_{2a} rats from weaning through gestation of F_{3a} offspring;

Tab J: Contains diet room records continued from notebook in Tab B. F. Martz, 5/11/87.

169 - 166 Additional data for rat reproduction study with teratology and dominant lethal portions (Mellon report #35-65, CDFA #169-099, 000712 and 027204), consisting of photocopies of laboratory notebooks or typed reports;

Record # 050955:

Tab A contains litter records for F_{2a} dams which delivered, consisting of birth dates, individual pup weights and the number of live or dead pups in the F_{3a} generation;

Tab B contains similar litter records for F_1 dams which delivered; Tab C contains individual body weight records for the gavage-treated F_{3a} groups;

Tab D contains similar information for feed-treated F_{3a} groups;

Record # 050442:

Tab E contains mating records for F_{2a} parents to produce the F_{3b} for the teratology portion of study;

Tab F contains individual F_{2a} dam sacrifice records for teratology portion of study, consisting of sacrifice calendar dates, the number of live or dead pups or resorption sites, the number of pups with gross anomalies and descriptions of observed anomalies, and litter weights;

Tab G contains a pathology report for an unidentified 1 month rat study at 150, 75, or 0 mg/kg/day via the feed;

Tab H contains pathology report for the sacrificed F_{3a} rats from the feed-treated groups, continued in Tab M for gavage-treated groups;

Tab I contains pathology report dated 3/21/72 for unidentified rat study using dietary dose levels of 200 or 0 mg/kg/day;

Tab J contains pathology report also dated 3/21/72 for unidentified rat study using oral gavage dose levels of 100 or 0 mg/kg;

Tab K contains pathology report dated 2/22/72 for teratology portion of reproduction study, with tabulation of skeletal and visceral observations;

Record # 050956:

Tab L contains report of uterine observations from dominant-lethal portion of reproduction study;

Tab M is a continuation of material in Tab H, and contains a pathology report dated 6/23/72 for the sacrificed F_{3a} pups from the gavage-treated groups;

Tab N contains duplicate pathology records for F_{3a} pups sacrificed on day 21 as well as records for F_{3a} rats sacrificed at 90 days of age;

Tab O contains pathology report dated 8/26/72 for F_{3a} rats sacrificed at 90 days of age, appears to be duplicate of some material in Tab N.

F. Martz, 5/19/87.

179 059543 "The Effect of Carbaryl (Sevin) on Reproduction of the Rat and the Gerbil." (Food and Drug Administration, Division of Pesticide Chemistry and Toxicology, DC, publication in Toxicol. Appl. Pharmacol. 19: 202-216 (1971), accepted 9/4/70, T. Collins et al.) Technical carbaryl, 99%, was fed in the diet to Osborne-Mendel rats at 0, 2000, 5000 or 10,000 ppm, 20/sex/group, three generations, two litters per generation or to Mongolian gerbils at 0, 2000, 4000, 6000 or 10,000 ppm, three generations, two litters. NOEL for reproductive effects < 2000 ppm (LDT) in both species with reduced weaning weights at all doses, decreased viability, survival, weaning indices at 5000 and 10,000 ppm in the rat with no animals at 10,000 for the second F1 mating or the F2 matings. No abnormalities reported; parental NOEL in the rat appeared to be 5000 ppm from the text; effects similar in the gerbil; no microscopic pathology included in the report; insufficient information to evaluate parental effects. Unacceptable, not upgradeable (no reproductive NOEL - all doses too high. (Gee, 9/30/88)

Previous summary: Although no study alone is adequate, the collective data provide sufficient information. The 1971 study indicated a possible adverse effect on reproduction at a dose not obviously toxic to the parental animals from the report. The publication by Collins et al., however, contains insufficient information for independent assessment of the parental toxicity. The later (1972) study, Record # 000712 and supplements, demonstrated a reproduction NOEL of 200 mg/kg in the feeding portion and a maternal NOEL of 25 mg/kg with no adverse developmental effect. Excessive postnatal mortality was seen in all groups, including the control so it was not a clear treatment effect. Since this study is much more complete and establishes NOELs, the conclusion is that there is no adverse reproduction effect without parental effects. From the 1972 study, it is likely that cholinesterase was markedly inhibited in the parental animals in the study by Collins et al. The collective data fill the data gap. Gee, 10/25/88.

NOTE: Record No. 170645 in 169-388 contains a statement that a new reproduction study is in progress with a due date of December, 2000. Gee, 10/1/99. This study was submitted in 169 - 410, record no. 182115 - see 1-liner above. Gee, 1/7/02.

RAT TERATOLOGY

**** 169-383 166125** A Carbaryl: Developmental toxicology study in the rat by gavage.@ (M. Repetto-Larsay, Study Director, Rhone-Poulenc Agro, Study SA 98070, October 21, 1998). Pregnant rats (CrI:CD(SD)BR), 25 per group, were given carbaryl (lot 208 115 110, 99%), at doses of 0 (0.5% methylcellulose 400), 1, 4 or 30 mg/kg/day by gavage, days 6 - 20 of gestation. Fetuses were given an external examination and approximately half were examined for visceral changes and half for skeletal effects. At 30 mg/kg/day, 18/25 dams had increased salivation within 20 minutes of dosing, disappearing within 1 hour and observed primarily between days 14 to 20 of gestation. In addition, maternal body weight was reduced statistically significantly at 30 mg/kg and fetal body weight was also reduced at 30 mg/kg. Maternal NOEL = developmental NOEL = 4 mg/kg/day (body weights, clinical signs in dams). ACCEPTABLE. No adverse effect. (Gee, 2/22/99)

169 - 099 000716 (With rebuttal and additional information in -154 and -162, 50438) "Results of a Three Generation Reproduction Study on Rats fed SEVIN in Their Diets," teratology of F_{3b}; Mellon Institute, report #28-53) 4/20/65; technical grade carbaryl, 99.8% pure, in the feed at 10, 2.5, or 0 mg/kg/day to 17-18 pregnant rats/level (F_{2a} of reproduction study) from prior to mating to sacrifice day 18-21; no soft tissue exams; no developmental toxicity, but no maternal MTD. UNACCEPTABLE and not upgradeable. J. Schreider, 5/10/85 and F. Martz,

5/6/87.

EPA One-liner: None in file.

169 - 154, Tab C, Section VII, pg. 8, Rebuttal of #000716 above: To quote: "The value of this study will not be discussed in detail as the dosage levels used...were so much lower than those used in a subsequent study." Agree. F. Martz, 5/6/87.

169 - 162 050438 Additional data included with rebuttal for #000716 above, consisting of photocopies of laboratory notebooks 911, 914, 945, and 951 as well as typed text and tables:

Tab A: Contains the "Diet Room Record" documenting the amounts of carbaryl and feed used for diet preparation.

Tab B: Individual body weights of F_0 , F_{1a} , and F_{1b} , and litter records for the F_0 and F_{1a} rats;

Tab C: Body weights and mating records of the F_2 generation ;Tab D: Litter records for pups of the F_2 females;

Tabs E, F, and G: Pathology summaries and raw data for fetuses, weanlings, and 90 day old individuals from the F_3 offspring. Additional data do not upgrade study although they indicate good documentation procedures. F. Martz, 5/19/87.

169 - 099 000715 (With rebuttal and additional information in -154 and -163, 50439) "Evaluation of the Teratogenic Potential of Insecticide SEVIN in Rats." (Mellon Institute, report #29-49, 7/28/66) Technical grade carbaryl, 99.7% pure, in the feed, was adjusted to give 500, 100, 20, or 0 mg/kg/day to 3 groups with 12/level each. The groups were treated: (1) throughout pregnancy or until weaning, (2) gestation days 0-7, or (3) gestation days 7-15 with one-half sacrificed days 19-21, the other half allowed to deliver with termination 21 days postpartum; gross and skeletal exams only.

MATERNAL: dose-related weight gain reduction, severest in group 1 (dosing throughout pregnancy);

DEVELOPMENTAL: none - no fetotoxicity or skeletal malformations; POSTNATAL: reduced live litter size and postnatal survival at 500 mg/kg (not considered a teratogenic effect);

MATERNAL NOEL = 20 mg/kg; FETOTOXIC NOEL = 100 mg/kg (based on reduced liveborn litter size); TERATOGENIC NOEL = 500 mg/kg (soft tissue exclusive).

UNACCEPTABLE and not upgradeable. J. Schreider, 5/10/85 and F. Martz, 8/6/87.

EPA One-liner: Teratogenic NOEL > 500 mg/kg (HDT), maternal LEL = 500 mg/kg (decreased weight gain), fetotoxic LEL = 500 mg/kg (mortality). Core grade: minimum.

169 - 130, 037910 Exact duplicate of #000715 above.

169 - 154, Tab C, Section VIII, pg. 8, Rebuttal of 29-49 above: Points are addressed as listed:

A. Rebuttal: "This design is more informative than [sic] the cook-book one in the guidelines..."

Response: We agree that the study design would provided more useful information overall than the standard Segment II type of teratology study, if all relevant parameters were covered, which they weren't.

B. Rebuttal: "It is notable that the dosage levels are remarkable and appropriate..."

Response: We agree. That the high dose level was a MTD is documented by the severely reduced body weight gain during gestation in that group.

C. Rebuttal: "The frequency of weighings and food consumption measurements, and these results for individual animals and dosage groups, may be found in the supplied Mellon Institute notebook 984 and 987."

Response: Located in -063, 50439.

D. Rebuttal: "The reviewer remarked: 'Sex and weight of fetuses not recorded.' The results

are summarized...in Table 29-88..."

Response: Table gives body weight of pups at weaning only. The fetal weights recorded at hysterectomy are still unaccounted for.

Comment: There is no evidence that soft tissue examinations were done. Therefore, the potential to cause visceral malformations remains unanswered by the data collected in this study.

Conclusion: The study is incomplete, unacceptable, and not upgradeable. F. Martz, 5/6/87.

169 - 163 050439 Additional data for rat teratology study #29-49, (CDFA #169-099, 715), consisting of photocopies of laboratory notebooks 911, 984, and 987:

Tab A contains "Diet Room Records" documenting the amounts of carbaryl and feed used in preparing diet blends.

Tab B contains individual female body weight values.

Tab C contains uterine examination observations of dams killed on day 20, and litter records on dams allowed to deliver and wean their offspring. Records consist of total pups in utero and dead or resorbed pups, anomalous observations, the dates of sacrifice or weaning, the number of pups born, on day 4 and 21, the individual pup weights according to sex on day 21, and any abnormalities.

While this volume contains good documentation of experimental conduct, it does not upgrade the report, mainly due to lack of feed analysis and soft tissue examinations. F. Martz, 5/12/87.

** 169 - 099 027204 (With rebuttal and additional information in -154 and -166, 50442) "Comparative Study of Dietary Inclusion versus Stomach Intubation on Three-Generations of Reproduction, on Teratology and on Mutagenesis." (Mellon Institute, report #35-65, 8/31/72). Technical carbaryl, 99.6% pure, in feed at 200, 100, 25, 7, or 0 mg/kg/day; by gavage in corn oil at 100, 25, 7, 3, or 0 mg/kg/day; in feed with corn oil equivalent at 100 or 0 mg/kg/day; to 6 month F_{2a} males and females 5 days/week (M->F) before and during mating/gestation; F_{3b} offspring examined;

FEEDING RESULTS: MATERNAL - decreased weight gain at 200 mg/kg, FETAL - incomplete ossification at 200 mg/kg; NOEL = 100 mg/kg maternal and fetal;

FEEDING/CORN OIL RESULTS: no effects at 100 mg/kg;

GAVAGE RESULTS: MATERNAL - cholinergic signs, mortality and reduced weight gain at 100 mg/kg, FETAL - reduced live litter size, more litters with resorptions, and incomplete ossification at 100 mg/kg; NOEL = 25 mg/kg maternal and fetal. Originally unacceptable (J. Schreider, 5/20/85) but upgraded to ACCEPTABLE (with major deviations). F. Martz, 5/87.

EPA One-liner for gavage: Teratogenic NOEL > 100 mg/kg (HDT), maternal LEL = 100 mg/kg (decreased weight gain, cholinergic signs, mortality), fetotoxic NOEL = 100 mg/kg (decreased live fetuses). Core grade: minimum.

EPA One-liner for feeding: Teratogenic NOEL > 200 mg/kg (HDT), maternal LEL = 200 mg/kg (decreased weight gain), fetotoxic NOEL > 200 mg/kg. Core grade: minimum.

154, Tab C, Section XI, pg. 11, Rebuttal of above study. Registrant's rebuttal and CDFA's response is similar to that given in "REPRODUCTION RAT, 35-65" below. We agree with rebuttal. In spite of major deviations from guidelines, the data appear to have been gathered in a manner scientifically valid and with good documentation. Total "weight of evidence" supports the absence of teratogenic potential. In my opinion, no new significant information would be gained from a study conducted according to current guidelines. Therefore, the teratology data gap is filled. F. Martz, 5/6/87.

166, 050422; Additional data for #027204 above; see -166 entry under "REPRODUCTION RAT (Mellon Report #35-65)."

169 - 131 to 133, 037925-27 "Teratology Study - SEVIN, Vitamin A, Aspirin and Malathion." (Litton, 6/23/72.) Technical carbaryl, 99.6% pure, was fed at 7000, 4000 or 0 ppm (approximately 375 or 200 mg/kg) to timed pregnant Sprague-Dawley females (Flow Labs; plug day=0), 20/level, days 6-15 with sacrifice on day 18, 1/3 fetuses visceral, remaining skeletal. No developmental toxicity, maternal weight gain can not be assessed from data presented, but data "...do not appear to show any evidence of maternal toxicity." NOEL>7000 ppm (approximately 375 mg/kg). F. Martz, 12/11/85 and 8/7/87.

EPA One-liner: NOEL = 375 mg/kg (HDT). Core grade: supplementary.

RABBIT TERATOLOGY

** 169-389 170646 A Developmental toxicity evaluation (with cholinesterase assessment) of carbaryl administered by gavage to New Zealand White rabbits.@ (R. W. Tyl, M. C. Marr and C. B. Myers, Research Triangle Institute, RTI No. 65C-7297-200/100, 6/3/99.) New Zealand White rabbits, 22/dose group, were given carbaryl (batch 208115110, 99% purity) by gavage at 0 (0.5% aqueous methylcellulose), 5, 50 or 150 mg/kg body weight/day on days 6 through 29 of gestation. Animals were sacrificed on gestation day 30. Dose selection was based on a range-finding study with 100 mg/kg as the high dose. Plasma cholinesterase was inhibited to 41% of control and RBC cholinesterase was 80.1% of control (not statistically significant) at 100 mg/kg. In the definitive study, body weight gain was reduced at 150 mg/kg, being 47% of control. Total body weight, however, was not significantly lower. Plasma cholinesterase was 46% and 32% of control at 50 and 150 mg/kg/day, respectively. Red blood cell cholinesterase was 81% and 73% of control at these doses. These values were statistically significant. At 150 mg/kg, fetal body weight was reduced, being 90% of control. There were no other developmental affects reported as related to treatment by the authors. There were two fetuses in two litters with agenesis of the gall bladder (10%, p = 0.27 by Fisher=s Exact) and 4 fetuses from three additional litters reported as having gall bladders A half normal size.@ These incidences were compared with 0/18 for the concurrent controls. The historical control incidence for agenesis of the gall bladder included in the report indicated 1/187 litters (0.53%). Maternal NOEL = 5 mg/kg (cholinesterase inhibition). Developmental NOEL = 50 mg/kg (reduced fetal body weight) No adverse effects. ACCEPTABLE. (Gee, 9/24/99)

Report not in CDFA file, but study by Robens (FDA), "Teratologic studies of carbaryl, diazinon, noree, disulfiram, and thiram in small laboratory animals," was published in Toxicol. Appl. Pharmacol. 15: 152-163 (1969).

EPA One-liner: Teratogenic, fetotoxic, and maternal NOEL all > 200 mg/kg by oral gavage (HDT). Core grade: minimum.

Report not in CDFA file, but study by Murray et al, "Teratogenic potential of carbaryl given rabbits and mice by gavage or by dietary inclusion," was published in Toxicol. Appl. Pharmacol. 51: 81-89 (1979).

EPA One-liner: Teratogenic, fetotoxic, and maternal NOEL all > 200 mg/kg by oral gavage (HDT). Core grade: minimum.

MOUSE TERATOLOGY

Report not in CDFA file, but study by Murray et al, "Teratogenic potential of carbaryl given rabbits and mice by gavage or by dietary inclusion," was published in Toxicol. Appl. Pharmacol. 51: 81-89 (1979).

EPA One-liner for gavage: Teratogenic and fetotoxic NOEL > 150 mg/kg (HDT), maternal LEL = 150 mg/kg (decreased weight gain, cholinergic signs). Core grade: minimum.

EPA One-liner for feeding: Teratogenic NOEL > 1166 mg/kg (HDT), fetotoxic LEL = 1166 mg/kg (decreased weight), maternal LEL = 1166 mg/kg (decreased weight gain). Core grade: minimum.

TERATOLOGY DOG

169 - 099 000714 "Sevin - Safety Evaluation by Feeding to Female Beagles From Day One of Gestation Through Weaning of the Offspring." (Woodard Res. Corp., 1/22/69) "Sevin technical grade," 99.8% pure, in the feed at 12.5, 5.0, 2.0, or 0 mg/kg/day, gestation day 1 through weaning at 6 weeks of age; increased stillbirths at 12.5 and 5 mg/kg; decreased birth weights and reduced survival to weaning at 12.5 mg/kg; inconclusive treatment-related malformations. UNACCEPTABLE and not upgradeable because of numerous deficiencies. J. Schreider, 5/10/85 and F. Martz, 8/4/87

EPA One-liner: Teratogenic NOEL = 2 mg/kg (LDT), teratogenic LEL = 5 mg/kg - (umbilical hernia, cleft palate, gastrointestinal abnormalities), Maternal NOEL < 2 mg/kg - (dystocia). Core grade: supplementary.

130, 037911: Exact duplicate of #000714 above.

No Record Number. Smalley, H. E., J. M. Curtis and F. L. Earl. A Teratogenic action of carbaryl in beagle dogs. Published in Toxicology and Applied Pharmacology 13: 392 - 403 (1968) (Division of Pharmacology and Toxicology, Food and Drug Administration, U. S. Department of Health, Education and Welfare) Technical grade carbaryl (lot 5072, 99.9%) was fed in the diet to beagle dogs at 0, 3.125, 6.25, 12.5, 25 or 50 mg/kg/day. Females were mated when in estrus with one male on day 1 and a second male on day 3. Dosing began on a Wednesday between day 3 and day 6 after mating. With the exception of 6 dogs, all were allowed to give birth and the pups weaned at 8 weeks. Following weaning, they were sacrificed and autopsied. The number of females per dose group varied between 16 for concurrent controls and 8 at the highest dose. There were no clinical signs or differences in body weight with treatment compared with the controls. Dams were also necropsied at week 8 postpartum. Although pup weights were similar at birth, weight gain was lower in all test groups (data by graph only). The percent conception ranged from 81% for controls to 37% for the 50 mg/kg/day group. The incidence of dystocia was increased in all treatment groups, being 3/group at 3.125, 6.25, 25 and 50 mg/kg and 5/18 at 12.5 mg/kg/day but with no clear dose response over the 16-fold difference in doses. The percent of pups born alive at 50 mg/kg was zero (0). The percent weaned was also decreased in the treatment groups but no cause of death was established. The litters with pups with abnormalities was increased with treatment above 3.125 mg/kg, being 0/13, 0/7, 1/7, 3/16, 3/6, and 1/2, control through high dose. The historical control value was 3/313. The authors state that the difference between 12.5 mg/kg and 25 mg/kg was not statistically significant. The percent of pups with abnormalities was 0, 0, 9, 18, 13 and 14% with increasing dose compared with a historical control value of 0.1%. The most serious effect was failure of the liver to develop. Also, a number of pups had openings in the ventral abdominal wall. Cholinesterase activity was not measured. **Possible adverse effects.** Maternal NOEL < 3.125 mg/kg/day based on dystocia incidence due to atonic uterine musculature. Developmental NOEL = 3.125 mg/kg/day (litter and pup incidence of abnormalities). The study indicates maternal and developmental toxicity but has limitations in terms of interpretation due to the small group sizes and the lack of a dose response for dystocia in dams over a 16-fold range in dose. SUPPLEMENTAL. (Gee, 10/22/99). EPA One-liner: Teratogenic NOEL = 3.1 mg/kg (LDT), teratogenic LEL = 6.3 mg/kg (lack of tail,

agenesis of external genitals, failure of pubis and ischium to develop, abdominal fissures, visceral agenesis), maternal NOEL < 3.1 mg/kg (dystocia). Core grade: Supplementary.

TERATOLOGY MONKEY

Report not in CDFA file, but an unpublished 1974 gavage study is listed with EPA One-liners: Teratogenic NOEL > 20 mg/kg (HDT), maternal NOEL > 20 mg/kg. Core grade: minimum.

TERATOLOGY GUINEA PIG

169 - 099 000713 (With rebuttal and additional information in -154 and -164, 50440); "Study of Guinea Pig Teratology of SEVIN fed in the Diet versus Stomach Intubation." (report #34-81; Mellon Institute, 11/30/71) Technical grade carbaryl, 99.6% pure, in the feed at 300, 200, 100, or 0 mg/kg/day, or by oral gavage in corn oil at 200, 100, 50, or 0 mg/kg/day, on single or multiple day "windows" from day 10 through 24 (plug day = 1), with sacrifice day 34-35; MATERNAL: reduced weight gain and death at 200 mg/kg gavage; FETAL: no malformations or clear evidence of fetotoxicity in spite of maternal toxicity. GAVAGE NOEL = 200 mg/kg for developmental, 100 mg/kg for maternal; FEEDING NOEL = 300 mg/kg for developmental and maternal. UNACCEPTABLE but has useful information. J. Schreider, 5/10/85 and F. Martz, 8/7/87.

EPA One-liner for gavage: Teratogenic NOEL 200 mg/kg (HDT), maternal LEL = 200 mg/kg (decreased weight gain, mortality), fetotoxic NOEL > 200 mg/kg.

EPA One-liner for feeding: Teratogenic NOEL > 300 mg/kg (HDT), maternal NOEL > 300 mg/kg, fetotoxic NOEL > 300 mg/kg.

Core grade for both: minimum.

169 - 154, Tab C, Section IX, pg. 9: Rebuttal of #713 above. Comments are as follows:

Rebuttal: "The purpose of this study was to determine the potential teratogenicity to guinea pigs by two routes of oral administration and at maternally lethal and sublethal concentrations" [in order to assess the results of Robens (1969) showing that 300 mg/kg administered to guinea pigs by capsule caused skeletal defects albeit with 38% maternal mortality]. "Note: It is inappropriate to compare the protocol design ["teratogenic window" dosing] of this study to the routine FIFRA teratology guidelines."

Response: This was an exploratory rather than "standard" protocol study, but the various periods of organogenesis were covered by sufficient animals when the study is taken as a whole. Moreover, no fetal effects were seen in the absence of maternal toxicity at oral gavage dose levels approaching the LD₅₀ established in a preliminary study for this strain of guinea pig. Considering that such treatment was more rigorous than dietary exposure, the absence of frank teratogenicity is noteworthy. Report by itself is still unacceptable, but rebuttal is accepted based on "weight of evidence." F. Martz, 5/8/87.

164, 050440; Additional data included with rebuttal for #713 above, consisting of photocopies of laboratory notebooks 1129 and 1138, as well as typed tables and reports:

Tab A: Contains the "Diet Room Record," documenting the amounts of carbaryl and feed used for diet preparation;

Tab B: Litter records consisting of the dams' sacrifice dates, the number of live or dead fetuses, resorption sites, individual fetal weights according to sex, and a description of gross anomalies if present;

Tab C: Pathology report dated 10/15/71 consisting of gross and microscopic observations of the livers and kidneys from dams receiving the top dietary or gavage

dose levels as well as the respective controls;

Tab D: Pathology report dated 9/3/71 consisting of skeletal examination findings;

Tab E: Pathology report dated 12/1/71 consisting of soft tissue examination findings;

Tab F: Pathology raw data records.

(F. Martz, 5/19/87).

TERATOLOGY - GENERAL SUPPORTIVE INFORMATION

169 - 155, Tab B, no record #; Correspondence dated 5/13/85 from EPA (Douglas D. Campt) to Union Carbide (J. S. Lovell) concerning carbaryl registration standard. Among several points raised, EPA maintained its request for a repeat of the 1958 chronic dog study which was unacceptable due to major deficiencies, and extended the due date to 5/87 [Note that the new report was completed 3/18/87, received by Medical Toxicology 5/11/87, and reviewed and accepted 5/12/87]. EPA rescinded its request for a repeat dog teratology study (listed in the Registration Standard), stating that "The agency has concluded that carbaryl would not constitute a potential teratogenic hazard to humans based on the overall weight of numerous (24) teratology studies that have been conducted. We also believe that the dog is not an appropriate model to perform a teratology study and relate it to humans." **NOTE that EPA reconsidered this matter in 1986 and "concluded that it was needed" (Pesticide and Toxic Chemical News, 4/30/86).

169 - 155, 050430 An undated position paper from Drs. J.G. Wilson, A. Koestner, and C.H. Williams (recognized experts), evaluating the teratologic potential of carbaryl, with appropriate references. In their opinion, "On the basis of these animal studies, carbaryl could not be classified as a general teratogen." I agree. F. Martz, 5/87.

Regarding positive responses in dog studies at 5 mg/kg and above, they regard that "This seemingly unique response of the beagle dog to carbaryl may in part be explained by certain metabolic peculiarities of this species with respect to this compound. The pathways for metabolism of carbaryl differ somewhat among mammalian species, but the dog stands alone in conjugating carbaryl directly, being unable to liberate 1-naphthol or to hydroxylate the parent compound (Khera, 1976). The National Institute for Occupational Safety and Health (NIOSH) in an exhaustive study of the safety of carbaryl in the workplace (Criteria for a Recommended Standard for Carbaryl, 1976), has concluded that: 'Present studies show that the metabolism of carbaryl in the dog differs from that in humans, monkeys, rats, and guinea pigs so it is unwarranted now to extrapolate from dogs to humans regarding the teratogenic potential of carbaryl.'" They agree "...with NIOSH that it would be inappropriate to use data from the dog in [developmental] safety evaluations applicable to man." F. Martz, 5/12/87.

169 - 130, 037915-24; Exact duplicate of 50430 above.

169 - 155, 050431 A 1976 EPA review/position paper from Dr. Neil Chernoff regarding reproductive and teratogenic potential of carbaryl, with appropriate references. In his opinion, "I feel that with the exception of the dog, in cases where severe maternal toxicity has not been observed there have been no consistent adverse reproductive or fetotoxic effects induced by carbaryl. The positive effects seen in the dog must be evaluated in light of its reported unusual metabolism. In the other species where positive effects have been shown, these effects must be considered in terms of maternal toxicity induced by the treatment, and the extremely high dose levels used. I feel that the use of such experiments which test for the maximum potential of a compound to induce effects is necessary to indicate types of effects to be looked for at lower dose levels (and such studies are regularly done in my laboratory). I do not feel that such

studies should be afforded important consideration in the overall toxicological evaluation of safety for the continued use of carbaryl. I feel, therefore, that the evidence to date does not indicate that continued use of carbaryl would pose a reproductive or fetotoxic threat to man." Based on the current weight of evidence, I agree. F. Martz, 5/12/87.

See Summary of Toxicology Data dated September 14, 1987 prepared by F. Martz with Note: The conclusion of Dr. Martz was that the data gap for teratology studies in a second species was filled with a second review by J. Parker.

GENE MUTATION

EPA One liner: There are (at least) 18 gene mutation assays. Although most had deficiencies, REAG accepted them collectively to demonstrate weakly positive response (EPA-600/6-81-001, January, 1981). These 18 studies are not on file at CDFA for independent review. In March, 1990, CDFA did not consider the data gap as filled because of the incomplete data base on file compared with that of EPA. Subsequent communication with the registrant (see 169-206) indicated these studies were not available for submission. The data gap status has been changed to filled. Gee, 7/31/90.

** 196 085660 "Mutagenicity Test on Carbaryl (Technical) in the Ames Salmonella/Microsome Reverse Mutation Assay." (Hazleton Laboratories America, Kensington, MD, HLA Study No. 10862-0-402, 9/6/89) Carbaryl technical, lot # 87191, 99.3% purity; tested with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100, triplicate plates, two trials; with and without Aroclor 1254-induced male Sprague-Dawley rat liver activation; Trial 1: 0 (DMSO), 5, 10, 50, 100, 500, 1000 ug/plate ; Trial 2: 0 (DMSO), 10, 50, 100, 500, 1000, 2000 ug/plate. **No evidence of increase in reversion rate.** Acceptable. (Gee, 2/28/90)

** 196 085658 "Mutagenicity Test on Carbaryl (Technical) in the CHO/HGPRT Forward Mutation Assay." (Hazleton Laboratories America, Kensington, MD, HLA No. 10862-0-435, 11/6/89) Carbaryl technical, lot 87191, 99.3% purity, was tested with CHO-K1-BH₄ in vitro with and without Aroclor 1254-induced rat liver activation. There was a single culture per concentration, 2 trials. Without activation, trial 1: 0 (DMSO), 0.001, 0.01, 0.03, 0.05, 0.08, 0.1, 0.15, 0.2, 0.3 (T) mg/ml; trial 2: 0 (DMSO), 0.01, 0.05, 0.1, 0.15, 0.2, 0.25 (T), 0.3 (T) mg/ml; with activation, trial 1: 0 (DMSO), 0.01, 0.05, 0.08, 0.1, 0.15, 0.2, 0.3 (T) mg/ml. In trial 2, only 1 concentration could be scored due to cytotoxicity with a new lot of S9; trial 3: 0 (DMSO), 0.001, 0.005, 0.01, 0.02, 0.04, 0.06, 0.08, 0.1 (T), 0.13 (T). **No reproducible increase in forward mutations.** Acceptable. (Gee, 2/28/90)

200 090474 Revised report of 085658.

169 - 457 209660 Duplicate of 085658

CHROMOSOMAL ABERRATION

169 - 099, 027202 (with rebuttal and additional data in -154, and -166, 050442, 050956); "Comparative Study of Dietary Inclusion versus Stomach Intubation on Three-Generations of Reproduction, on Teratology and on Mutagenesis," dominant lethal portion; Mellon Institute, report #35-65, 8/31/72; technical carbaryl, 99.6% pure in feed at 200, 100, 25, 7, or 0 mg/kg/day; by gavage in corn oil at 100, 25, 7, 3, or 0 mg/kg/day; in feed containing corn oil at

100 or 0 mg/kg/day; 5 days/week (m->f); F_{2a} males withdrawn at 7 months old, mated weekly for 10 weeks:

FEEDING RESULTS: No dose-related or consistent differences, NOEL = 200 mg/kg;

FEEDING/CORN OIL RESULTS: no effects at 100 mg/kg, NOEL = 100 mg/kg;

GAVAGE RESULTS: Significant reduction in mean implants or viable fetuses at 100 mg/kg in week 8 mating only, 12.5 vs 14.0 control or 11.5 vs 14.0 control, respectively. Not regarded to be meaningful. NOEL = 100 mg/kg/day.

Originally reviewed as unacceptable without useful data (J. Schreider); now is UPGRADEABLE with additional information. F. Martz, 8/20/87.

EPA One-liner: None on file.

165 050441 Supplement to 027202.

166, 050442 & 050956; see "Reproduction Rat (Mellon report #35-65)" above for listing of entries.

169 - 179 059544 "UC 51762 - Inclusion in the Diet of Rats for Three Generations and Dominant Lethal Mutagenesis Studies." Supplemental to Record # 027202. (Carnegie-Mellon Institute, Report 42-65, 7/2/79) Positive control data with TEM given by i.p. injection to male Fischer 344 rats and mated with 1 female for each of three weekly periods. TEM caused

increased resorptions in all three weeks. Supplemental data. No change in status of # 027202. Gee, 10/3/88.

**** 169 - 196 085657** "Mutagenicity Test on Carbaryl Technical: In an in vitro Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells." (Hazleton Laboratories America, Kensington, MD, HLA Study no. 10862-0-437, 8/31/89) Carbaryl technical, Lot # 87191, 99.3%; tested with CHO-WBL cells in vitro for chromosomal aberrations; without S9, at 0 (negative and solvent), 7.5, 10, 25, 50 or 75 ug/ml, 17.5 hours incubation and 20-hour harvest, duplicate cultures; with Aroclor 1254-induced Sprague-Dawley rat liver S9 activation at 0 (negative and solvent), 150, 200, 250 or 300 ug/ml, duplicate cultures, 2 hour incubation and harvest at 20 and at 30 hours; harvest times based on a preliminary study with BrdUrd staining for determination of cell cycles in 27.5 hours total; no increase in aberrations without activation; **possible adverse effect** with activation - increase in aberrations/cell, % cells with aberrations and % cells with >1 aberration at both harvest times. Acceptable. (Gee, 2/27/90)

EPA One liner: EPA considers the following studies acceptable for filling the chromosome mutation data gap: Can. J. Genet. Cytol., 8:481-501, 1966.; Cytologia, 30:175-181, 1965; Cytologia, 33:334-337, 1968; Flora (Jena), 160:443-439, 1971; Archiv za Poljoprivedne Naake, 25:128-138, 1973. The studies cited by EPA above need to be submitted for independent review. Gee, 3/90.

**** 169 - 0458 209661** " Carbaryl: Induction of micronuclei in the bone marrow of treated mice." (Marshall, R., Corning Hazleton (Europe), Study number 198/89-1052, March 13, 1996) CD-1 mice were treated with carbaryl (lot OP 9450293, 99.9%) in 0.5% carboxymethylcellulose at doses of 0, 50, 100 or 200 mg/kg/day, for two consecutive days, with 5/sex/dose sacrificed after a further 24 or 48 hours. Cyclophosphamide was used as the positive control and was functional. At 200 mg/kg, animals showed lethargy which lasted about 2 hours after the first dose with eye closure in 3 females, eye secretions in 1. Weight loss was seen in 2 males and 10 females at the high dose. For each animal, 2000 polychromatic erythrocytes were scored for micronuclei and the PCE/NCE reported. There was no induction of micronuclei by carbaryl in this study. ACCEPTABLE with no adverse effect. (Gee, 3/2/04).

DNA DAMAGE/REPAIR AND OTHER

EPA One liner: There are 3 DNA repair assays (Mutation Research, 42:161-174, 1977; Mutation Research, 38:293-302, 1976; Mutation Research, 22:121-126, 1974) which collectively fill the data gap. These studies are not on file at CDFA and need to be submitted. Gee, 3/5/90.

** 196 085659 "Mutagenicity Test on Carbaryl Technical in the in vitro Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay." (Hazleton Laboratories America, Kensington, MD, HLA Study No. 10862-0-447, 11/22/89) Carbaryl technical, lot 87191, 99.3% purity; tested with primary rat hepatocytes from male Fischer 344 rats, two trials; trial 1: 0 (DMSO), 0.5, 1.0, 2.5, 5, 10 or 25 ug/ml; trial 2: 0 (DMSO), 5.0, 7.51, 10, 15, 20 or 25 ug/ml; scored 150 cells per concentration from triplicate coverslips; **no evidence of unscheduled DNA synthesis**. Acceptable. (Gee, 2/28/90)

** 169 - 0456, 0466 209659, 212614 "Investigation of the potential for protein- and DNA-binding of carbaryl." (Sagelsdorff, P., Ciba-Geigy, Basel, CB93/52, R013980, April 28, 1994) Covalent binding of ¹⁴C-carbaryl to chromatin protein and to DNA was determined using male CD-1 mice. There were 5 groups of 4 - 6 per group treated as follows: Group 1 received one dose of 75 mg/kg of radioactive carbaryl by gavage; group 2 were fed 8000 ppm for 13 days, then given radioactive carbaryl in a single dose at 75 mg/kg body weight; group 3 were untreated and used for controls of the extraction procedures; group 4 were fed 8000 ppm for 14 days and group 5 were untreated. Groups 4 and 5 were not processed [see 169-455, 209658]. Urinary excretion was measured for a single animal from groups 1 and 2 over 24 hours and found to be 33 and 31%, respectively, of the administered dose. Fecal excretion was not measured. Livers from 2 animals of the same group were pooled for processing. Livers were homogenized, chromatin precipitated, deproteinated and DNA further purified on hydroxylapatite, dialyzed and precipitated with ethanol. Chromatin protein was precipitated with acetone and dissolved in 1% SDS several times. Radioactivity was determined by LSC. Binding was determined as a function of mg of protein and of DNA. The pmol/mg binding to protein ranged from 7 to 11, with no difference between groups 1 and 2. For DNA, binding (dpm/mg) was <5.99 with an 80% counting efficiency and a limit of detection of 2.7 cpm over background. The Covalent Binding Index (CBI) was calculated to be <0.1 as a maximum DNA-binding ability. This result gives no indication for a genotoxic potential for carbaryl mediated by DNA binding. The CBIs for strong hepatocarcinogens (such as aflatoxin B1) are magnitudes higher. Record 212614, 169-0466, contains the publication detailing the methods used in the study. ACCEPTABLE with no indication of DNA binding. (Gee, 7/20/04)

169 - 0466 212614 "The relevance of covalent binding to mouse liver DNA and to the carcinogenic action of hexachlorocyclohexane isomers." (Sagelsdorff, P., W. K. Lutz and C. Schlatter, publ. in *Carcinogenesis* 4:1267 - 1273 (1983). This submission was related to the one above, record 209659, giving details of the methods used in the isolation and quantitation of DNA and protein for binding analysis. (Gee, 7/20/04)

169 - 399 177756 D. Bigot "Validation on Transgenic Mice - p53 Knockout Mice - to Predict Rodent Carcinogenicity." (Rhone-Poulenc Agro, Study SA 97040, 11/10/99) Male mice, C57Bl/6 Tac-[KO]Trp53N5-T, heterozygous for p53 tumor suppressor gene, were compared with wild type male mice for response to the urethane, a genotoxic compound known to induce vascular tumors in lifetime studies in mice, and to d-limonene, not carcinogenic in mice. There were 20 mice per group, given 0, 1, 10 or 100 mg/kg/day of urethane by gavage for at least 180 days or d-limonene at 250 mg/kg/day. Wild type mice were given vehicle only.

Body weights and food consumption were recorded as were clinical signs. At necropsy, all major organs were examined, selected organs weighed, and tissues prepared for histopathological examination. At 100 mg/kg urethane, only 3 animals survived to termination with 2 dying at 10 mg/kg. A total of 18/20 mice at 100 mg/kg urethane had vascular neoplasms, predominantly in the liver, at 181 – 184 days. At 10 mg/kg, 1/20 had a vascular tumor and none were seen at 1 or in the vehicle control group. The results supported urethane as a model for vascular tumors in p53 knockout mice induced by a genotoxic carcinogen. D-Limonene exposure resulted in hyperplasia of the non-glandular stomach but was considered negative for tumor induction. This study was submitted as support for record no. 177755 with carbaryl. No worksheet. (Gee, 3/28/06)

169 – 398 177755 F. Chuzel "Carbaryl 6-Month Carcinogenicity Study in p53 Knockout Mice by Dietary Administration." (Rhone-Poulenc Agro, Study SA 98155, 7/8/99) Carbaryl (99% purity) was fed in the diet to groups of 20 male mice for at least 180 days. Mice were C57Bl/6 Tac fBR-[KO]p53N4, heterozygous for the p53 tumor suppressor gene. Doses were 0, 10, 30, 100, 300, 1000 or 4000 ppm (mean achieved doses were 0, 1.76, 5.21, 17.5, 51.6, 164.5 and 716.6 mg/kg/day). The purpose was to better understand tumors seen in the earlier study, record 123769, N. Hamada, HWA 656-138, 5/20/93 [see above under mouse oncogenicity]. This strain of knockout mice has been shown to respond to genotoxic carcinogens in a shorter time frame than in a usual bioassay, forming tumors in the first six months of life, before the spontaneous incidence increases. See record 177756 above. Body weight, food consumption and clinical signs were recorded. Selected organs were weighed and tissues prepared for histopathological examination. All control and high dose animals were examined as were all decedents. No treatment-related deaths were reported. There were some effects on body weight and food consumption at 1000 and 4000 ppm. The major non-neoplastic finding was the presence of an accumulation of "globular deposits" in the umbrella cell layer of the urinary bladder. The total incidences were: 0/20, 0/20, 0/20, 11/20, 20/20, 20/20 and 20/20, control through high dose. The appearance was transparent, slightly yellow and birefringent at 100, 300 and 1000 ppm and smaller but with a red-brown color at 4000 ppm. The severity of the accumulation increased with dose. There was no reported local irritation or hypertrophy of the bladder epithelium. Relative organ weights were increased in heart, liver and kidney at 4000 ppm and for kidney at 1000 ppm as well. The NOEL = 30 ppm (5.2 mg/kg). There was no treatment-related evidence of neoplastic or preneoplastic changes in vascular tissue or any organs examined. Several spontaneous neoplasms were found with none, however, present at 4000 ppm. This study did not demonstrate a genotoxic potential for carbaryl. Supplemental study. No worksheet. (Gee, 3/29/06)

NEUROTOXICITY, HEN

169 - 134 037928 (with rebuttal and additional information in -154 and -156, 50432) "Comparison of the Demyelination Potential of SEVIN and Triorthocresyl Phosphate in Chickens, with Observations on the effects in Liver, Kidney, and gastrocnemius Muscle Tissue." (Mellon Institute, report #21-87, 9/15/58) No brain, spinal cord or sciatic nerve effects at 3 g/kg, subcutaneously, but results were inconclusive because of weak TOCP effect also at 3 g/kg. F. Martz, 5/4 and 8/7/87 (no worksheet).

EPA One-liner: Negative at 2000 mg/kg (approximate LD₅₀). Core grade: minimum.

154, Tab C, Section I, pg. 1, and 169-156, 50432, rebuttal to 169-023, no record #; Rebuttal not necessary because study is not required, inasmuch as carbamates have no documented neurotoxic potential such as that exhibited by organophosphates. F. Martz, 8/7/87 (no worksheet).

NEUROTOXICITY, DEVELOPMENTAL, RAT

** 169 - 384 166126 "A developmental neurotoxicity study of orally administered carbaryl, technical grade, in the rat." (K. Robinson and B. Broxup, ClinTrials BioResearch Ltd., Quebec, Project 97391, 9/23/97). Sprague-Dawley Crl:CD(SD)BR rats were treated with carbaryl, 99.1% purity, by oral gavage at doses of 0 (aqueous 0.5% carboxymethylcellulose/0.1% Tween 80), 0.1, 1.0 or 10 mg/kg/day, day 6 of gestation through day 10 post partum. There were 26 per group for the developmental neurotoxicity phase and 6 per group for cholinesterase determinations. Both F0 adults and F1 generation were examined by a "modified" Functional Observation Battery. Additional parameters for pups were also recorded including motor activity, brain measurements, development (tooth eruption, eye opening, vaginal opening, preputial separation) and gross and microscopic pathology. Effects on F0 dams at 10 mg/kg/day included autonomic effects and tremors seen during the treatment period, inhibition of RBC, whole blood and brain cholinesterase at 10 mg/kg. Maternal NOEL = 1 mg/kg/day. In the F1 generation, there were no effects on FOB, motor activity, startle response, avoidance, water maze times, body weight, brain morphometric measurements, or pathology. Developmental neurotoxic NOEL = 10 mg/kg/day. No positive control data were included or cited. Unacceptable but upgradeable with information concerning appropriate positive control studies. No adverse effects. (Gee, 2/16/99)
Note: A considerable body of positive control studies conducted at BioResearch has been submitted. See below. These studies upgrade the developmental neurotoxicity study to ACCEPTABLE status. No new worksheet. (Gee, 7/27/04)

169 - 391 170648 Supplement to 169-384 166126 Supplement date of June 1, 1999. Authors were K. Robinson and B. Broxup. At the request of US EPA for additional morphometric measurements to assist in the interpretation of the occasional statistically significant differences in specific areas of the brain between the control and high-dose pups and adults, the measurements were repeated. Evaluation of the mid- and low-dose groups was stated as not possible due to the lack of appropriate control tissues with the passage of time. The reevaluation confirmed some of the original findings. These were, again, discounted as treatment-related by the authors based on such criteria as unilateral finding, not seen in both pups and adults, found in one sex only, and not statistically significant based on the adjusted P-value. This submission did not address the positive control data requested by DPR for an upgrade of the study. SUPPLEMENTAL. (Gee, 9/10/99).

NEUROTOXICITY, RAT

169 – 396 177090 "An experimental functional observational battery validation study with carbaryl in Wistar rats" (Wahle, M. S., Bayer Corporation, Stilwell, KS, Report 109406, 7/26/00) The purpose of the study was to validate the procedures of the Functional Observational Battery using untreated animals and animals exposed to a substance with known effects, carbaryl, to serve as positive control data under FIFRA guidelines for neurotoxicity studies. Four technicians were involved. Procedure: Male Wistar Hanover rats (total of 40) were subjected to FOB observations before treatment, 10 animals per technician. Six per group were then given 0 (vehicle: 5% (v/v) ethanol and 5% (v/v) Cremophor EL), 15 or 30 mg/kg carbaryl (99%) by intraperitoneal injection, single dose. At 20 to 90 minutes post-dosing, animals were subjected to an FOB and observed by the four technicians. Compound-related effects at 15 mg/kg included a variety of autonomic signs, alterations in CNS excitability, neuromuscular effects, decreased sensorimotor responses and alterations in activity. The

effects at 30 mg/kg were increased in incidence and severity. The observations of each technician were reported and compared. With a few exceptions, there was good agreement among the observers. The study supported the validity and sensitivity of the procedures and training of personnel. Supplemental study. (Gee, 9/20/2000)

** 169 - 341 142602 " An acute study of the potential effects of a single orally administered dose of carbaryl, technical grade, on behavior and neuromorphology in rats." (Brooks, W., K. Robinson and B. Broxup, Bio-Research Laboratories, Quebec, Project 97389, October 24, 1995) Carbaryl (lot 201085006, 99.1%) was given in a single oral dose by gavage at nominal doses of 0 (Aqueous 0.5% carboxymethylcellulose/0.1% Tween 80), 10, 50 or 125 mg/kg to twelve Sprague-Dawley (CrI:CD®(SD)BR) rats per sex per dose. Dosing was done over 3 days with 4/sex/group dosed each day. Observations included a FOB, motor activity, and brain weight and measurements over a 14 day period following dosing. The observations were made predosing, on day 0 at 0.5 hours for the FOB and 50 to 90 minutes after dosing for motor activity. These observations were repeated on days 7 and 14. On day 15, six per sex per dose were perfused and histopathology performed on the control and high dose animals. NOEL for clinical signs and FOB = 10 mg/kg. There was, however, a statistically significant decrease in motor activity on day 0 at 10 mg/kg, being 177.2 ± 59 versus 221.7 ± 51.3 for males and 314.3 ± 101.6 versus 393.8 ± 127.6 for females. Motor activity was measured over a total of 60 minutes. There was also a statistically significant lower body temperature in females at 10 mg/kg (37.46^{***} versus 38.52 in controls) but this was discounted as not being a reflection of neurotoxicity and as comparable to the historical control range of 37.6 to 38.8°C. Males at 10 mg/kg had temperatures comparable to controls, day 0. Among the observations on day 0 were tremors, lower body temperature, decreased motor activity with the effects being greater at 125 mg/kg than at 50 mg/kg. All animals were comparable to controls by day 7. Positive control data for FOB and neuropathology were submitted on a CD. Acceptable. (Gee, 7/26/04)

** 169 - 0459, 0465 209662, 212613 " A 13 week study of the potential effects of orally administered carbaryl, technical grade, on behavior, neurochemistry and neuromorphology in rats." (Robinson, K. and B. Broxup, Bio-Research Laboratories, Ltd., Quebec, Laboratory ID project 97390, R014070, September 24, 1996) Sprague-Dawley CrI:CD®(SD)BR male and female rats were given technical grade carbaryl (99.1%) by oral gavage for 90 days at 0 (0.5% (w/v) carboxy-methylcellulose/0.1% Tween 80), 1, 10 or 30 mg/kg/day nominal doses. A total of 27/sex received each dose. Twelve per sex per dose were used for the behavior evaluations prestudy and week 4, 8 and 13. Groups of 5/sex/dose were used for cholinesterase prestudy and each of weeks 4, 8 and 13 with brain cholinesterase also being determined. Cholinesterase activity was reported for RBC, whole blood, plasma, left hemisphere and selected regions of the brain. Cholinesterase activity was lower in most samples at 10 and 30 mg/kg/day for blood and brain. The major FOB observations at 10 and 30 mg/kg were decreased pupil size, tremors of the head/body/limbs and reduced rearing of females at 4 and 8 weeks. At 30 mg/kg/day, additional observations included increased salivation. Decreased body temperature was noted in females at 10 and 30 and in males at 30 mg/kg/day. Decreases in motor activity were noted on occasion at 30 mg/kg/day. Some clinical findings were of lower incidence at week 13 than at earlier times. Six/sex/group were perfused for neuropathology, including brain measurements. There were no treatment-related histopathological findings in the nervous system. NOEL = 1 mg/kg/day (tremors, decreased pupil size, reduced activity and cholinesterase activity). Record 212613 contains a brief description of the method used for cholinesterase measurements and the individual data for blood parameters, specifically hematocrit, used in RBC cholinesterase calculations. ACCEPTABLE. Positive control data were submitted on a CD. (Gee, 7/26/04)

POSITIVE CONTROL STUDIES submitted on a compact disc. Selected pages of each study have been printed and are on file in the Medical Toxicology Branch under CC 105, carbaryl.

Project 29537: Compact disc. "An acute neurotoxicity study of the effects of orally administered DDT and trimethyltin chloride in rats." (Beyrouy, P., Bio-Research Laboratories, Quebec, Canada, 11/4/94) Male rats were given doses of 0, 112.5 mg/kg DDT or 9 mg/kg trimethyltin chloride, single oral dose. They were examined prestudy, day 0 (following dosing) and days 7 and 14 for FOB, motor activity and neuropathology following perfusion (controls and TMT only). All essential parameters of home cage, handling, arena, FOB, grip strength, foot splay and pathology were examined and reported, including all individual data. The expected responses were noted. DDT caused tremors, decrease in rearing, were hyper-reactive when handled, diarrhea, increased hindlimb splay and decreased activity counts on day 0 compared with controls. For TMT, with the exception of a slightly lower temperature, all values were similar to controls on day 0. On day 7, however, TMT caused increased rearing and locomotor activity in the arena and 2/12 had "shakes when handled" and 2/12 were "difficult to handle." On day 14, TMT animals had increased forelimb grip strength and increased hindlimb splay (not seen on day 7). On both days 7 and 14, TMT caused increased activity counts compared with controls and DDT exposed rats. The major finding with TMT was the expected neuropathology of the central and peripheral nervous system in perfused animals, day 15. No gross changes were recorded but microscopic findings included necrosis of neurons, occasionally associated with neuronophagia and gliosis, in sections of the brain. In the peripheral nervous system, slight to moderate changes were seen including axonal degeneration and swelling, myelin splitting/bubbling, Schwann cell hypertrophy/hyperplasia and interstitial edema. This report is an acceptable study to support the acute and subchronic neurotoxicity studies with carbaryl. No worksheet. (Gee, 7/21/04) Duplicate of 52093-080, record 156318.

Project 29538: CD "A subchronic neurotoxicity study of the effects of orally administered acrylamide in rats." (Beyrouy, P., Bio-Research Laboratories, Quebec, Canada, 11/4/94) Male Sprague-Dawley rats (12/group) were given either vehicle (water) or 40 mg/kg/day of acrylamide by oral gavage. Doses were repeated for 12 days. Animals were examined prestudy, days 7 (predosing) and 14. Parameters included the FOB, motor activity and neuropathology. Animals were sacrificed on day 15 with 6/group being chosen randomly for perfusion and subsequent pathological exam. One male given acrylamide died before completion of the study. Mean body weights were significantly lower with acrylamide throughout the study, being 280.8*** at day 14 versus 361.0 in controls. The major clinical observations with acrylamide were hypersensitive/aggressive behavior when handled (10/12) and abnormal gait (8/12). During the FOB on day 7, significant affects included hypotonic gait (8/12), decreased arousal (5/12), flaccid abdominal tone (6/12) and increased hindlimb splay. On day 14, all neuromuscular parameters were affected (flaccid muscle tone, ataxic gait, reduced fore and hindlimb grip, increased hindlimb splay, and decreased locomotor activity, arousal and rearing incidents in the arena, others). Motor activity was also reduced on both days 7 and 14. Neuropathological examination showed damage (e.g axonal degeneration) to the peripheral nerves, ganglia and roots and lesions in the CNS (degeneration/necrosis of purkinje cells of the cerebellum). This report is an acceptable study to support the acute and subchronic neurotoxicity studies with carbaryl. No worksheet. (Gee, 7/21/04). Duplicate of 52093 - 081, record 156319.

Project 29546: CD. "An acute neurotoxicity study of the effects of orally administered carbaryl and triadimefon in rats." (Beyrouy, P., Bio-Research Laboratories, Quebec, Canada, 11/4/94) Male Sprague-Dawley rats (12/group) were given a single oral dose by gavage of 0 (0.5% carboxymethylcellulose/0.1% Tween 80 (w/v)), triadimefon at 100 mg/kg or carbaryl (lot 81-25B, 97%) at 40 mg/kg. Animals were evaluated for motor activity and FOB prestudy, day 0 (day of

treatment, 1 - 1 1/2 hours post dosing), and days 7 and 14. All animals were discarded on day 15. No necropsy/histopathology was performed. Body weights were comparable in all groups. Triadimefon treatment resulted in significant increases in locomotor activity, rearing and arousal in the arena on day 0. With carbaryl, day 0, there were significant increases in tremors (9/12), salivation (8/12), and pupil constriction (pinpoint, 8/12), decreased rearing in the arena (1.8 versus 8.9 in control), overall gait incapacity (9/12), decreased locomotor activity (7/12) and depressed arousal (8/12), others. Grip strength and hindlimb splay were comparable to controls. There was a significant decrease in motor activity, day 0, with carbaryl, being overall (60 minutes) 60.7*** versus 235.1 in controls. Triadimefon activity was increased to 544.8, as statistically significant. By day 7, all groups were essentially comparable. The study gave the anticipated results with these two compounds. This report is an acceptable study to support the acute and subchronic neurotoxicity studies with carbaryl. No worksheet. (Gee, 7/21/04)
Duplicate of 52093 - 083, record 156321.

Project 97104: CD. "A benchmark study of the acute toxicity of DDT (1,1-bis[p-chlorophenyl]-2,2,2-trichloroethane) in the albino rat." (Beyrouy, P., Bio-Research Laboratories, Quebec, Canada, 6/16/92) Pairs of male Sprague-Dawley rats were given a single oral dose of DDT by gavage at doses of 0 (corn oil), 50, 75, 112.5, 168.8, 253.1 or 379.7 mg/kg. They were observed for 1 week. At 379.7 and 253.1, both animals died within 6 and 21 hours, respectively. All rats showed head, body and/or limb tremors commencing 4 hours after dosing. Clonic-type convulsions were seen in 1 animal each at 112.5 and 379.7mg/kg, just prior to death. Other signs included hyper-reactivity to sound, piloerection and nasal/ocular discharge. The "benchmark" dose (highest non-lethal dose) was 168.8 mg/kg. This study is supplemental as a positive control study. No worksheet. (Gee, 7/22/04)

Project 97107: CD. "A benchmark study of the acute toxicity of carbaryl in the albino rat." (Beyrouy, P., Bio-Research Laboratories, Quebec, Canada, 6/16/92) Pairs of male Sprague-Dawley rats were given carbaryl (lot 56-98A, P5-84, 98%) as a single dose of 0 (aqueous 0.5% (w/v) carboxymethylcellulose/0.1% Tween 80), 125, 250, 500 or 1000 mg/kg by oral gavage. Animals were observed for 1 week. At 1000 mg/kg, both animals died on the day of dosing and 1 animal at 500 mg/kg was dead 2 days after dosing. All treated rats showed tremors of the head, body and/or limbs beginning about 10 minutes after dosing. Autonomic signs (salivation, lacrimation, urinary staining) were seen within 6 hours. Other signs seen on the day of treatment included muzzle staining, abnormal respiratory rate/abnormal sounds/gasping, exophthalmus and flattened body position. All treated groups lost weight from day 0 to day 1. Generally, findings were no longer noted 1 to 2 days following treatment. The "benchmark" dose (highest non-lethal dose) was 250 mg/kg. This study is supplemental as a positive control study. No worksheet. (Gee, 7/22/04)

Project 97108: CD. "A time of peak effect study of an acute dose of carbaryl in the albino rat." (Beyrouy, P., Bio-Research Laboratories, Quebec, Canada, 10/22/92) Pairs of Sprague-Dawley male rats were given a single dose of carbaryl (lot No. 56-98A, 98%) at 0 (aqueous 0.5% carboxymethylcellulose/0.1% Tween 80), 25, 80 or 250 mg/kg. Animals were assessed with an abbreviated FOB at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours post-dosing. Animals were observed for a total of 7 days, including body weight measurements. Rats given 250 mg/kg showed decreased arousal and locomotor activity with the largest effect at 1 - 1.5 hours. Other findings included incapacitated gait, tremors, salivation, lacrimation (beginning at 4 hours), urinary staining (beginning at 4 hours) and reduced respiration. At 80 mg/kg, locomotor activity was decreased with the greatest effect from 0.5 to 3 hours. Arousal was reduced the most from 0.5 - 1 hour. Other findings at 80 mg/kg included incapacitated gait, tremors, salivation and reduced respiration. At 25 mg/kg, animals were comparable to controls. Body weight losses were seen at 80 and 250 mg/kg. NOEL = 25 mg/kg. The estimated peak time of effect was 0.5

to 1.5 hours post-dosing. Supportive information for neurotoxicity studies. No worksheet. (Gee, 7/22/04)

Project 97109: CD "An acute study of the potential effects of orally administered carbaryl on behavior in rats." (Beyrouy, P., Bio-Research Laboratories, Quebec, Canada, 11/3/92) Groups of 12 male Sprague-Dawley rats were given a single dose of 0 (aqueous 0.5% carboxymethylcellulose/0.1% Tween 80), 12.5, 40 or 125 mg/kg carbaryl (lot 56-98A, P5-84, 98%) by oral gavage. No analysis of dosing material. Animals were evaluated using a FOB and motor activity at pretest and days 0 (day of treatment), 1, 7 and 14. Histopathology was limited to sections of the brain and abnormal tissues. No animals died or were sacrificed. Body weight at 125 mg/kg was significantly lower on days 1 (9.5%) and 7 (6%), resulting from a mean loss of 27 g from day 0 to day 1. For the FOB at 125 mg/kg, day of treatment, there were significant increases in tremors (12/12 vs. 0), gait incapacity (11/12 vs. 0), and autonomic signs (salivation, miosis). They showed reduced locomotor activity (12/12), arousal (11/12), decreased defecation, abnormal responses to sensory tests and others. At 40 mg/kg, animals showed increases in tremors (11/12), salivation and decreased locomotor activity (11/12 v 2/12 in control), arousal (11/12), toe/tail pinch and decreased defecation. At 12.5 mg/kg, defecation was also reduced on day 0. By day 1, all groups were similar. Forelimb and hindlimb grip strength was reduced at 125 mg/kg, day 0, and hindlimb at 40 mg/kg. Foot splay was significantly increased for both groups. Body temperature was lower for all groups, being 38.0, 37.3*, 34.9** and 34.3** for control through increasing dose. Group mean total activity counts, day 0, were lower at 40 and 125, being 209, 207, 43.3*** and 23.7***, control through increasing dose. There were no significant differences on days 7 and 14. There were no apparent treatment-related histopathology findings in the brain. NOEL = 12.5 mg/kg, based on FOB findings on the day of treatment. This report supports the definitive acute and subchronic neurotoxicity studies with carbaryl. No worksheet. (Gee, 7/22/04)

Project 97110: CD. "A benchmark study of the acute toxicity of trimethyltin chloride in the albino rat." (Beyrouy, P., Bio-Research Laboratories, Quebec, Canada, 6/26/92) Pairs of male Sprague-Dawley rats were given a single oral dose by gavage at 0 (corn oil), 5.3, 8, 12, 18 or 27 mg/kg. They were observed for 7 days. On day 2, they were subjected to a limited FOB including arena/handling. The brain from each surviving animal was retained and examined (6 coronal sections) using hematoxylin and eosin and Kluver Barrera stains. All animals at 12 mg/kg and above died before termination of the study but lived long enough to yield data. Both males at 12 and at 27 and one at 18 displayed tremors by day 3, lasting until death. Aggressive behavior was noted at 12 mg/kg on day 3 of handling. The FOB on day 2 showed tremors, decreased locomotion, impaired gait at 27 mg/kg. By day 7, rats given 12 mg/kg showed a large decrease in body weight (-103 g). Histopathology of the brain showed neuronal necrosis of the limbic system (hippocampus, pyriform cortex, entorhinal cortex) at all TMT doses with the severity being greater at 12 mg/kg and above. The "benchmark" dose (highest non-lethal and adequate to cause neuropathology) was 8 mg/kg, single dose. This study provides neuropathology positive control data for the neurotoxicity studies with carbaryl. No worksheet. (Gee, 7/22/04)

Project 97111: CD: "A time of peak effect study of an acute dose of trimethyltin chloride in the albino rat." (Beyrouy, P., Bio-Research Laboratories, Quebec, Canada, 10/22/92) Pairs of Sprague-Dawley male rats were given single doses of trimethyltin chloride by oral gavage using doses of 0 (corn oil), 4, 6 or 9 mg/kg. Animals were given an abbreviated FOB predosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours post dosing. The FOB included locomotor activity and arena/handling observations. After 14 days, all animals were sacrificed and the brain retained for histopathology. Six coronal levels were stained with hematoxylin and eosin or Kluver Barrera stains. No clear time of peak effect was noted but arousal at 9 mg/kg was slightly

increased at all times and locomotor activity was increased. According to the author, this occurred between 5 and 7 hours post dosing. Histopathology of the brain showed neuronal necrosis of the limbic system (ammon's horn, pyriform cortex and entorhinal cortex) in all doses, with severity being greatest at 9 mg/kg. At 4 mg/kg, 1 of 2 showed slight pathology. This study provides neuropathology positive control data for the neurotoxicity studies with carbaryl. No worksheet. (Gee, 7/23/04)

Project 97112: CD. "A benchmark study of the acute toxicity of triadimefon in the albino rat." (Beyrouy, P., Bio-Research Laboratories, Quebec, Canada, 6/16/92) Pairs of male Sprague-Dawley rats were given triadimefon (lot 46-114A, 99%) in a single oral dose by gavage of 0 (aqueous 0.5% carboxymethylcellulose/0.1% Tween 80), 150, 300, 600 or 1200 mg/kg. Animals were followed for 7 days, being observed for clinical signs (0.5, 1, 2, 4 and 6 hours post dosing) and body weight. After 7 days, animals were terminated without necropsy. Both animals at 1200 mg/kg and 1 at 600 mg/kg were terminated on day 1 due to poor condition. All treated animals showed hyperactivity, starting within 0.75 hours of treatment, and "sniffing", beginning at 4 hours. Ataxia was seen at 300 mg/kg and higher, bizarre behavior (including self mutilation) at 600 mg/kg. Other effects were also seen. All treated animals had weight loss from day 0 to day 1, with overall weight gain over 7 days being lower. No NOEL was determined. The "benchmark" dose, defined as the highest non-lethal dose, was 300 mg/kg. This study is supplemental to the positive control data. No worksheet. (Gee, 7/23/04)

Project 97113: CD. "A time of peak effect study of an acute dose of triadimefon in the albino rat." (Beyrouy, P., Bio-Research Laboratories, Quebec, Canada, 10/22/92) Pairs of male Sprague-Dawley rats were given a single oral dose of triadimefon by gavage at doses of 0 (aqueous 0.5% (w/v) carboxymethylcellulose/0.1% Tween 80), 30, 100 or 300 mg/kg. Animals were examined at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8 and 24 hours post dosing using an abbreviated FOB (locomotor activity, arena/handling). After 7 days, animals were terminated and discarded without necropsy. Locomotor activity was increased from hours 1 - 8 post dosing with the largest difference being from 1.5 - 3 hours. Arousal was increased at 100 mg/kg, hours 1-5, and at 300 mg/kg, hours 1 - 8. There was marked weight loss days 0 - 1 at 300 mg/kg (35.5 g), resulting in lower body weight day 7. The overall peak time of effect was 1.5 - 3 hours post-dosing. This study is supplemental to the positive control data. No worksheet. (Gee, 7/23/04).

Project 97132: CD. "An acute study of the potential effects of orally administered triadimefon on behavior in rats." (Beyrouy, P., Bio-Research Laboratories, Quebec, Canada, 276 pages, 11/19/92) Groups of 12 male Sprague-Dawley rats were given a single oral dose of triadimefon (lot 46-114A, 99%) by gavage at 0 (aqueous 0.5% (w/v) carboxymethylcellulose/0.1% Tween 80), 30, 100 or 300 mg/kg. Animals were observed for 14 days, being assessed for motor activity and full FOB prestudy, day 0 (estimated time of peak activity - not stated) and days 1, 7 and 14. On day 15, animals were terminated and subjected to necropsy. The brain was retained from 6/group for possible future analysis. Motor activity was significantly increased in all groups. Rearing was increased at 300 mg/kg and arousal was increased at 100 and 300 mg/kg. There was no effect on temperature, grip strength or splay. Also, there were no gross necropsy findings. This study is supplemental to the positive control data. No worksheet. (Gee, 7/26/04)

Project 97134: CD. "An acute study of the potential effects of orally administered DDT [1,1-bis(p-chlorophenyl)-2,2,2-trichloroethane] on behavior in rats." (Beyrouy, P., Bio-Research Laboratories, Quebec, Canada, 303 pages, 11/20/92) Groups of 12 male Sprague-Dawley rats were given doses of 0 (corn oil), 11.3, 35 or 112.5 mg/kg in a single dose by gavage. The animals were evaluated by FOB and motor activity prestudy and on days 0 (at estimated time of peak effect - not stated), 1, 7 and 14. On day 15, 6/group were selected for perfusion and

neuropathological examination. The rest were examined for necropsy. There was no effect on body weight. On day 0, increase in tremors, difficulty of removal from home cage, muzzle staining, reduced tail pinch and delays for positional passivity test were noted at 112.5 mg/kg. Also, there was a reduction in arousal, pinna reflex, increased urination, diarrhea, and hyperreactivity to sound/increased auditory startle. On day 1, at 112.5 mg/kg there was a significant increase in locomotor activity, arousal and rearing. Hindlimb grip strength was lower at 112.5 mg/kg and body temperature was higher on day 0. No abnormal gross or neuropathology findings were reported. This report supports the definitive acute and subchronic neurotoxicity studies with carbaryl. No worksheet. (Gee, 7/26/04)

Project 97135: CD. "A subacute study of the potential effects of orally administered acrylamide on behavior and neuromorphology in rats." (Beyrouthy, P., Bio-Research Laboratories, Quebec, Canada, 225 pages, 11/13/92) Groups of 12 male Sprague-Dawley rats were given 10 doses over 14 days at 0 (water), 4, 13 or 40 mg/kg/day by gavage. Animals were evaluated using a FOB and motor activity. On day 15, 6 per group were selected for perfusion and control and high dose animals were evaluated for neuropathology. Brains were saved from the other 6/group for possible future evaluation. Body weight at 40 mg/kg was significantly lower (-12.9%) on day 14. The FOB on day 14 showed a significant increase in the incidence of ataxic gait, incapacitation and flaccid body/abdominal tone (10/12) at 40 mg/kg. There was also a reduction in fore and hindlimb grip strength (546.7 versus 735 g in controls), increase in hindlimb splay (11.1* versus 8.5 cm in controls), and a decrease in total activity counts (96.9 versus 238.7 in controls). No gross pathological findings but there was a decrease in brain width. Neuropathology also indicated degeneration of peripheral nerves, changes in cell nuclei and cell body cytoplasm (granularity) of spinal root ganglia at the high dose. Necrosis of the purkinje cells and vacuolation of the neuropil of the cerebellum were also noted at 40 mg/kg/day. This study provides neuropathology positive control data for the neurotoxicity studies with carbaryl. No worksheet. (Gee, 7/26/04).

Project 97136: CD. "An acute study of the potential effects of orally administered trimethyltin chloride on behavior, neuromorphology and neurochemistry in rats." (Beyrouthy, P., Bio-Research Laboratories, Quebec, Canada, 302 pages, 11/20/92) Groups of 12 male Sprague-Dawley rats were given a single dose of trimethyltin chloride at 0 (corn oil), 4, 6 or 9 mg/kg and followed for 2 weeks. Animals were evaluated with a FOB and for motor activity prestudy, day 0 (at estimated time of peak effect - not stated) and days 7 and 14. On day 15, 6 per group were sacrificed and given a necropsy with the brain removed for GFAP (glial fibrillary acidic protein) analysis in six regions of the brain and the other 6 in control and high dose were perfused for neuropathological evaluation and stained with hematoxylin and eosin, Kluver-Barrera and Holmes stains for light microscopy. Body weight at 9 mg/kg was lower on day 7. In the FOB, at 9 mg/kg, there was an increase in the incidence of rats lying on side/curled up in the home cage on day 0 (6/12). By day 7, locomotor activity, toe pinch response and vocalization were increased at 9 mg/kg. By day 14, locomotor activity remained increased. There was no difference in grip strength, foot splay or temperature. Motor activity was increased on days 7 (377 versus 202 in control group) and 14 (418 versus 216 in controls) at 9 mg/kg. There were no gross pathological findings related to treatment but neuropathological exam found neuronal necrosis and astrogliosis of the hippocampus and pyriform cortex of the brain. Changes in the peripheral nervous system, primarily in the sciatic and tibial nerves, lumbar dorsal root and lumbar dorsal root ganglion such as myelin splitting and bubbling were seen. There were significant increases in GFAP at the high dose for the cerebral cortex and striatum regions. This study provides neuropathology positive control data for the neurotoxicity studies with carbaryl. No worksheet. (Gee, 7/26/04).

Project 97162: CD. "An inter-observer reliability (IOR) study for qualitative functional

observational battery assessments in rats." (Beyrouy, P., Bio-Research Laboratories, Quebec, Canada, 88 pages, 11/18/92) Pairs of male Sprague-Dawley rats were treated with a single dose by gavage of DDT (100 mg/kg), carbaryl (100 mg/kg) or acrylamide (40 mg/kg). The animals were assessed by a group of 5 observers to assess major neurotoxic endpoints. All observers detected the expected findings within 1 grade for ranked data. The five observers were identified by a letter. The conclusion was that the observations would be suitable for studies and reliable if more than one observer was used in a given study. No worksheet. (Gee, 7/26/04).

See also 52093 - 082, record 156320, for a similar study of inter-observer reliability, 11/4/94, Bio-Research Laboratories project 29540, submitted with cyclanilide. Reviewed by Aldous, 10/8/97.

Project 97163: CD. "An inter-observer reliability (IOR) study for grip strength and hindlimb splay measurements in rats." (Beyrouy, P., Bio-research Laboratories, Quebec, Canada, 51 pages, 11/16/92) Ten male Sprague-Dawley rats were assigned to each of 5 observers. All animals had been tested on day -6 by a single experimenter. No differences were noted among the 5 observers for forelimb strength or hindlimb splay. There was, however, a difference for hindlimb strength. Following additional training, the results were comparable. No worksheet. (Gee, 7/26/04)

See also 52093 - 079 Record 156317 for a similar study on inter-observer reliability, 11/4/94, Bio-Research project 29539, submitted for cyclanilide and reviewed by Aldous, 10/3/97.

OTHER INFORMATION

169-390 170647 " Range-finding toxicity study in rats with carbaryl technical." (N. N. Hamada, Hazleton Laboratories America, Inc., Vienna, VA, HLA 656-137, 9/10/90). Carbaryl technical, lot 87191, 99.3% purity, was fed in the diet to Crl:CD7BR rats, 10/sex/group, as follows. Main study animals received 0, 50, 125, 500/4500, 1500/6000 or 3000 ppm for six weeks. The doses were increased after 3 weeks due to a lack of a compound effect. In the supplemental study, 10/sex/group received 0, 300, 6000, 12000 or 24000 ppm in the diet for 4 weeks followed by an extension for an additional 4 weeks (total of 8 weeks) due to a lack of sufficient treatment-related effects. In the main study, hematology and clinical chemistry parameters were measured including plasma, erythrocyte and brain cholinesterase at week 6. In the supplemental study, only cholinesterases were assayed at termination. Body weights were lower at ≥ 3000 ppm. Clinical signs were noted at 4500 and above including thin appearance, urine stains, hunched appearance and rough haircoat. At 12000 ppm, 3 females were found dead or sacrificed and at 24000 ppm, 1/sex were found dead. No cause of death was reported by the author but from clinical observations, mortality was probably treatment-related. The NOEL for cholinesterase inhibition was 300 ppm. Systemic NOEL = 1500 ppm (decreased body weight). Supplemental range-finding study. (Gee, 9/30/99)

023, 038359, 038177 and 038178; 1961 review article in Agricultural and Food Chemistry, 9:30-39, by Carpenter et al, summarizing: chronic rat and dog studies, Mellon reports #21-88 and #21-89, in -099, 719 and 718, respectively; mouse subcutaneous oncogenicity, Mellon report not on file; hen neurotoxicity study, Mellon report #21-87, in -134, 37928.

167, 050443; Exact duplicate of 169 - 023 above.

169 - 167, 050446 & -47: Journal article - Weil et al (1972). Current status of tests of carbaryl for reproductive and teratogenic effects. Toxicol. Appl. Pharmacol. 21:390-404. Covers rat reproduction and teratology studies in Mellon Institute reports:

#28-53, teratology and reproduction, in -099, 716;

#29-49, teratology, in -099, 715;

#35-65, reproduction (through F_{1a} only), in -099, 712. (No worksheet).

167, 050448 & -49: Journal article - Weil et al (1973). Comparative effect of carbaryl on rat reproduction and guinea pig teratology when fed either [sic] in the diet or by stomach intubation. in Toxicol. Appl. Pharmacol. 26:621-638. Covers rat reproduction/teratology/dominant lethal and guinea pig teratology studies in Mellon Institute reports:

#35-65, rat reproduction (all generations), teratology, and dominant lethal, in -099, 712, 27204, and 27202, respectively;

#34-81, guinea pig teratology, in -099, 713.

(No Worksheet).

023, 038365: One sentence summary of Mellon Institute chronic dog report #21-89, in -099, 718. Source of summary unknown.

023, 038363: One sentence summary of Mellon Institute rat reproduction report #28-53, in -099, #716. Source of summary unknown,

023, 038364: Two paragraph summary of Mellon Institute rat teratology report #29-49 and guinea pig teratology report #34-81, in -099, 716 or 713, respectively. Source of summary unknown.

023, 038366 and 038367: One paragraph summary of Mellon Institute rat reproduction report #35-65, in -099, 000712. Source of summary unknown.

169 - 155, 050427 Exact duplicate of 169-148, 046798, reviewed 10/27/86 by F. Martz. This is a literature review that states carbaryl is a primary neurotoxicant and cites 40 reports on acute toxicity in various species. Data from the open literature indicate that carbaryl can produce developmental toxicity and in some instances, teratogenicity. D. Shimer, 3/24/87.

148, 046798, Exact duplicate of 169-155, 050427, reviewed 3/24/87 by D. Shimer; Literature review of carbaryl entitled "Carbaryl: A Toxicological Review and Risk Analysis," by Morris F. Cranmer, in NeuroToxicology 7:247-332, 1986. This review article concerns material from published articles as well as unpublished information supplied by Union Carbide. Areas covered include neurotoxicity, acute toxicity, developmental toxicity, mutagenicity, immunotoxicity, oncogenicity, human exposure and toxicity, and cancer risk assessment of N-nitrosocarbaryl exposure. Twelve pages of references are provided which include the unpublished Union Carbide reports. F. Martz, 10/27/86.

55, Tab B, no record #; Correspondence dated 5/13/85 from EPA (Douglas D. Camp) to Union Carbide (J.S. Lovell) concerning carbaryl registration standard (no worksheet).

169 - 155, 050428 A review article on carbaryl entitled "Carbaryl: A Literature Review," by Michael E. Mont and Frederick W. Oehme, in Residue Reviews 80:1-6-4, 1981. Topics covered include chemistry, toxicity in target and non-target pests, birds, mammals, and humans, metabolism/ pharmacokinetics, environmental fate, interactions, analytical methods, and residues. Not reviewed in detail, no worksheet. F. Martz, 5/12/87.

55, 050429 Incomplete copy of EPA's Registration Standard for carbaryl, a partial duplicate of

that document located in 169-103, 12895 (no worksheet). F. Martz, 5/12/87.

103, 012895; Contains the Regulatory Position section of the EPA Carbaryl Registration Standard submitted to CDFA by Union Carbide, and is a partial duplicate of material located in 169-155, 50429 (no worksheet). J. Schreider, 5/6/85.

SUBCHRONIC (4-week), DERMAL, RAT

169 - 413 186206 Austin, E. W. "4 Week repeated-dose dermal toxicity study with carbaryl technical in rats." (Covance Laboratories, Covance 6224-268, 3/8/02) Carbaryl technical (99.49%) was applied to the skin of Crl:CD®(SD)IGS BR rats, 10/sex/group, at 0 (reverse osmosis water), 20, 50 or 100 mg/kg/day, 6-7 hours per day, 5 days per week, for 4 weeks. The test material was applied to moistened skin, under gauze, to approximately 10% of the body surface. The purpose of the study was to evaluate red blood cell and brain cholinesterase activity following dermal application. Body weight, food consumption and dermal effects were evaluated. A slight atonia was noted on occasion in 1/10 males and 4/10 females ($p = 0.043$) at 100 mg/kg/day. Body weight gain was statistically significantly lower days 5-12 in males at 100 mg/kg, being 24 ± 7.7 versus 33 ± 6.9 in control males. Total body weights, day 12, in males were not significantly different. RBC cholinesterase was evaluated before the daily application on days 1, 8, 15, and 22 and within 1 hour after dosing removal on days 5, 12, 19 and 26. Brain cholinesterase was determined in the right half of the brain following sacrifice on day 26. The method used for cholinesterase determination was not cited. The mean RBC activity was 10 to 15% lower than controls, especially in samples following dosing. At day 26, there were no differences among the control and treatment groups for RBCs. The mean brain cholinesterase activity, day 26, was 15% lower at 50 and 100 mg/kg/day in males and 24% lower at 100 mg/kg/day in females. Cholinesterase NOEL = 20 mg/kg/day. Dermal NOEL = 100 mg/kg/day in males and 50 mg/kg/day in females (atonia). Supplemental data. (Gee, 4/11/02) (Revised 7/23/04, Gee, for male body weight effect)

169 - 414 186207 Austin, E. W. "4 Week repeated-dose dermal toxicity study with SEVIN® XLR PLUS in rats." (Covance Laboratories, Covance 6224-267, 3/7/02) Sevin XLR Plus, 44.82% (wt/wt) was applied to approximately 10% of the body surface of Crl:CD®(SD)IGS BR rats, 8/sex/group, at 0 (water), 20, 50 or 100 μ l/kg/day, 6-7 hours/day, 5 days/week, for 4 weeks. The test material was applied neat to the skin and covered. The purpose of the study was to evaluate red blood cell cholinesterase activity following dermal exposure. Body weight, body weight change, food consumption and dermal irritation were evaluated and were negative for treatment-related effects. RBC cholinesterase was measured before daily exposure on days 1, 8, 15 and 22 and within 1 hour after dosing removal on days 5, 12, 19 and 26. No brain cholinesterase activity was measured. No necropsy was performed. In females at 100 μ l/kg/day, there was a 12% inhibition (statistically significant at $p \leq 0.05$) on days 5 and 12 after dosing but not on days 19 and 26, which were comparable with controls. In males at the high dose, there were no samples with significant inhibition. Due to the mild inhibition and the lack of consistency, the relationship of the inhibition to test article administration was uncertain. The method used for cholinesterase activity was not cited and the selection of doses not justified. The NOAEL = 100 μ l/kg/day with a clear NOEL not established. Supplemental data. (Gee, 4/11/02).

169 - 415 186208 Austin, E. W. "4 Week repeated-dose dermal toxicity study with SEVIN® 80S in rats." (Covance Laboratories, Covance 6224-266, 3/8/02) Sevin 80S (lot C8I168025A, 80.07%) was applied to approximately 10% of the body surface of

CrI:CD®(SD)IGS BR rats, 8/sex/group, at doses of 0 (reverse osmosis water), 20, 50 or 100 mg/kg/day, 6-7 hours per day, 5 days/week, for 4 weeks. The material was applied as a powder to moistened skin and covered. The purpose was to evaluate red blood cell cholinesterase activity. Body weight, food consumption, dermal irritation and clinical signs were evaluated and there were no treatment-related findings. RBC cholinesterase activity was measured pretest, before dosing on days 1, 8, 15 and 22 and within 1 hour after removal of the dosing material on days 5, 12, 19 and 26. No brain cholinesterase was measured and no necropsy performed. RBC cholinesterase activity was inhibited (8 to 20%) at 50 and 100 mg/kg when samples were taken within the hour after dosing. With samples taken before dose, there was no consistent pattern of inhibition. Cholinesterase NOEL = 20 mg/kg/day. The method of cholinesterase analysis was not cited and the doses were not justified. Supplemental data. (Gee, 4/11/02)

SUBCHRONIC (4-week), ORAL, MOUSE

169-401 177758 "Carbaryl - Preliminary 28-day toxicity study in the male TSG p53 wild type mouse by dietary administration." (M. Dange, Rhone-Poulenc Agro, Studies SA 97499 and SA 97538, April 10, 1998). Carbaryl (batch 208115110, 98.4%) was fed in the diet to C57BL/6 TSG p53 wild type male mice, 6 weeks of age at start of dosing. In study SA 97499, diets of 0, 160, 1000 or 8000 ppm were fed to 10 mice per group. In study SA 97538, diets of 0, 2000 or 4000 ppm were fed to 10 male mice per group. Mean achieved intake in mg/kg/day was, with increasing diet concentration, 0, 35.7, 222, 424.4, 935.6 and 2107.3. On day 29 or 30, all mice were necropsied. The organ weights for liver and kidneys were recorded. No histopathology was performed. The primary data collected were for body weight, mortality, clinical signs and organ weight. No clinical signs or mortality were noted in either study. The major results were for body weight. At 8000 ppm, mice lost about 14% of their initial body weight in the first week (20.16** versus 23.26) and did not recover by the end of the study. At 4000 ppm, mice had lower body weights between 5.5 and 8.5% (mean of 6.5%) over the 4 weeks with a slight loss in week 1 (21.19** versus 21.54). No effect on body weight was seen at 2000 ppm or lower. The other significant effect was on the relative liver weight at 8000 ppm, which was statistically higher than controls (+ 15%) but absolute organ weights were comparable. The relative liver weights for 4000 ppm (+ 11%**) and 2000 ppm (+ 5%*) were also higher, but not the absolute weights. No treatment-related macroscopic organ findings were seen at necropsy. Supplemental study. No worksheet. (Gee, 2/26/04)

ACUTE ORAL, RAT

169 - 0463 212610 "Research report: A study on the effect of substrate concentration and detection wavelength on the blood cholinesterase assay in the rat." (Brooks, W., study director, Bio-Research Laboratories, Ltd., 10/19/95, project 29803) Male rats (5/group) were given vehicle or 30 mg/kg carbaryl (technical grade, 99.1%) in a single dose by oral gavage. Blood was sampled at 45-50 minutes (estimated peak of activity) and whole blood and plasma cholinesterase activities were determined. The assay was conducted at either 480 or 405 nm and the substrate was used as supplied or diluted 1:5 with water. Results indicated that the absolute enzymatic activity (U/L) increased 4.3 to 6 fold when the wavelength was changed from 480 nm to 405 nm (both undiluted and diluted substrate) but the ratio of test samples to controls did not change significantly with change in wavelength. Dilution of the substrate had no significant effect at either wavelength. Hematocrit was used to calculate the RBC cholinesterase activity. Supplemental study. (Gee, 7/20/04)

169 - 339 142599 "An acute benchmark-dose toxicity study of orally administered carbaryl, technical grade, in rats." (Brooks, W. and B. Broxup, Bio-Research Laboratories, Quebec, Project 97387, October 12, 1995) The benchmark dose was defined as the highest non-lethal dose. Carbaryl (lot 201085006, 99.1%) was given by gavage to 2/sex Sprague-Dawley Crl:CD®(SD)BR rats at 10, 50, 100, 250, 500 or 1000 mg/kg in 0.5% (w/v) carboxy-methylcellulose/0.1% Tween 80, in a single dose at 10 ml/kg. Dosing was followed by a three-day observational period for clinical signs/mortality. Body weights were recorded on days 0, 1 and 3. No necropsy was performed. Analytical data for test article were included. A detailed physical exam was performed on day 0 predosing and at 0.5, 1, 2, 4 and 8 hours post dosing and on days 1, 2 and 3. Results: At 1000 mg/kg, all animals were found dead within 24 hours. At 500 mg/kg, 1/2 males and 2/2 females were found dead within 24 hours. All animals survived at 250 mg/kg = benchmark dose. Clinical observations were seen in all groups above 10 mg/kg/day. Within 30 minutes, both sexes, all rats at ≥ 50 mg/kg exhibited slight to severe salivation, tremors of head, body and/or limbs. Additional observations seen in some or all groups at 50 mg/kg and above included lacrimation, periorbital staining, urogenital staining, decreased activity, decreased respiration rate, abnormal breathing sounds and weakness. With a few exceptions, such as staining, decreased activity and weakness, many of the signs were no longer observed 1 day after dosing. All groups except 10 mg/kg showed weight loss between day 0 and day 1. Supplemental study. No worksheet. (Gee, 2/26/04)

169-338, 464 142593, 212611 " A time of peak effects study of a single orally administered dose of carbaryl, technical grade, in rats." (Brooks, W. and B. Broxup, Bio-Research Laboratories, Quebec, Project 97388, October 12, 1995) Carbaryl (lot 201085006, 99.1%) was given in a single oral dose by gavage at 0 (0.5% carboxymethylcellulose/0.1% Tween 80), 10, 50 or 125 mg/kg to Sprague-Dawley (Crl:CD®(SD)BR) rats of both sexes. There were three/sex/dose in the behavioral phase with termination after 24 hours and 15/sex/dose in the cholinesterase phase with 3/sex terminated at 0.5, 1, 2, 4, or 8 hours post dosing. In the behavioral phase, animals were given an abbreviated FOB predose and at 0.5, 1, 2, 4, 6, 8 and 24 hours after dosing. The FOB consisted of observations in an arena, which included locomotor activity, gait, tremor, twitches, convulsions, behavior, respiratory rate, lacrimation, salivation, staining and diarrhea. These animals were evaluated for cholinesterase activity at 24 hours. The cholinesterase activity of whole blood, plasma and whole brain was measured. The RBC activity was calculated. FOB findings were noted at 50 and 125 mg/kg whereas only 1 male at 10 mg/kg showed muzzle staining prior to sacrifice at 0.5 hours. Some FOB findings decreased in frequency and/or severity with time after dosing. By 8 hours, at 50 mg/kg in males, one animal showed muzzle and urinary staining only. At 125 mg/kg, 8 hours, males showed lacrimation, muzzle and urinary staining. By 8 hours in females, muzzle staining and urinary staining were still present at 50 and 125 mg/kg. At 24 hours, muzzle and urinary staining were still visible in both sexes at 125 mg/kg. The NOEL for clinical signs/FOB = 10 mg/kg, both sexes. Evaluation of the cholinesterase activity indicated that the time of peak difference in activity was at 0.5 and 1 hour. By 2 hours, whole blood activity at 10 mg/kg was comparable to controls. At 50 mg/kg, activity in females was comparable to controls by 4 hours, whether compared to concurrent vehicle controls or to predose values. Recovery was slightly slower in males. Activities in whole blood and plasma were comparable to controls at 24 hours. At 125 mg/kg, all activities were still lower than controls at 24 hours. In the brain, activity was comparable to controls at 24 hours for 10 and 50 mg/kg but still lower at 125 mg/kg, being 77% of control in males and 65% in females. Since there were only 3/sex at each sampling time, statistics were not done. Data for the hematocrits used to calculate the RBC activity were submitted in 169-464. The conclusion was that the times of peak effects were at 0.5 and 1 hour, based especially on the results at the lower doses. Supplemental study. (Gee, 2/27/04)

169 - 340, 467 142600, 212615 " An acute study of the time course of cholinesterase

inhibition by orally administered carbaryl, technical grade, in the rat." (Brooks, W. and B. Broxup, Bio-Research Laboratories, Quebec, Project 97392, October 23, 1995) Carbaryl, technical grade, lot 201085006, 99.1%, was given by oral gavage in a single dose at 0 (0.5% carboxymethylcellulose/0.1% Tween 80), 10, 30 or 90 mg/kg in 10 ml/kg, to male and female Sprague-Dawley (CrI:CD®(SD)BR) rats. There were 24 per dose group with 6/sex/dose sacrificed at 1, 8, 24 or 48 hours after dosing. Blood, brain and several brain regions were processed for determination of cholinesterase activity. Whole blood and plasma activities were measured and RBC activity was calculated from these measurements after determining hematocrits. The regions of brain were: left hemisphere for whole brain, and regions from the right hemisphere were frontal cortex, hippocampus, cerebellum and caudate/putamen. Clinical signs were recorded. No clinical signs were reported for 10 mg/kg animals. At 30 and 90 mg/kg, signs included tremors (slight at 30, moderate to severe at 90 mg/kg), salivation, staining of fur and wetness in various areas on the day of treatment with an occasional observation at 90 mg/kg up to 2 days (termination of the study). NOEL = 10 mg/kg, based on clinical signs. At one-hour post dose, cholinesterase activity was statistically lower in all samples from the 30 and 90 mg/kg groups and in most samples at 10 mg/kg. By 8 hours, all samples at 10 mg/kg were comparable to control and by 24 hours, all samples from 30 were comparable to controls. By 48 hours, all samples were also comparable to controls. ChE NOEL < 10 mg/kg at 1 hour, 10 mg/kg at 8 hours, 30 mg/kg at 24 hours and \geq 90 mg/kg at 48 hours. The data for the individual hematocrits used in calculating the RBC activity submitted in 467. Supplemental study. (Gee, 2/27/04 and 7/26/04)

METABOLISM

** 169 - 0453 209656 " Metabolism of ^{14}C -carbaryl in rats (preliminary and definitive phases)." (Struble, Craig B., Hazleton Wisconsin, HWI 6224-184, R013850, August 5, 1994) ^{14}C -Carbaryl was given to HSD:SD rats at a low dose of approximately 1 mg/kg (Groups A, B and C) and a high dose of 50 mg/kg (Group D) with 5 per sex per group. The low dose was given to Group A by iv, to Groups B and C by oral gavage and the high dose by oral gavage. Group C had received 14 days of dosing with non-labeled carbaryl prior to the radio-labeled carbaryl. Results of analyses of the urine and feces indicated that metabolism was similar for both sexes and doses. Mass balance for all dose groups ranged from 97.6% to 104% for males and 96.1 to 103% for females. Comparison with the iv group indicated approximately 95% or greater absorption. Urine was the primary route of excretion with 84.5% to 95.0% [including cage wash/wipe] of the administered dose and with 6.98% to 12.5% in the feces. None was found in CO_2 . Less than or equal to 0.91% of the administered dose was found in the carcass plus tissues. Most of the carbaryl was excreted within 12 hours for the low dose and 24 hours for the high dose. Metabolites were identified with reference standards using TLC, HPLC and LC/MS. Four conjugated metabolites were found in urine. Identified metabolites accounted for 75% in urine and 1% in feces, with the major one in feces being dihydro-dihydroxy carbaryl. Three major pathways were observed: arene oxide formation with metabolism to dihydro-dihydroxy carbaryl and conjugation, carbamate hydrolysis to form 1-naphthol and oxidation of N-methyl moiety. A metabolic pathway was proposed. ACCEPTABLE. (Gee, 3/3/04)

160 - 0454 209657 " Carbaryl: Investigation of the metabolism of [^{14}C]-carbaryl in the 15 month-old male rat following chronic dietary administration, final report." (Totis, M, Rhone-Poulenc Agrochimie, study SA 95288, R014082, December 19, 1996, amended on October 3, 1997) CD male rats, 15 months of age at initiation of dosing, were divided into 5 groups: Group A, single dose of 50 mg/kg [^{14}C]-carbaryl and followed for 168 hours with urine and feces collected; Group B, fed control diet for 83 days followed by 7 daily doses of labelled carbaryl at approximately 2 mg/kg; Groups C and D, fed at 250 ppm or 7500 ppm in the diet followed by 7 daily doses of labelled carbaryl at approximately 2 mg/kg and Group E, added later, and fed at

1500 ppm for 83 days followed by the 7 doses of radioactive material. Achieved doses were 9.89, 250.71 and 58.96 mg/kg/day over the 13 weeks of feeding. Five males in groups B, C, D and E were fed these doses for 90 days and were used for histopathological examination and for biochemical analyses for total glutathione, protein, glutathione peroxidase and glutathione-S-transferase in the liver. There were 23 metabolites in urine and twenty in feces, including carbaryl. In urine, the major components were UMET/11 (Glucuronide of dihydro-dihydroxy carbaryl), UMET/18 (α -Naphthyl β -D-glucuronide, sodium salt) and UMET/23 (sulfo conjugate of naphthol). The major portion of the administered dose was excreted in the urine within the first 24 - 48 hours with greater than 65% of administered doses. The feces contained considerably less radioactivity with some carbaryl found as well as a number of metabolites (not identified). Tissue levels were low with the kidneys, in general, containing the most residual activity. Terminal body weights at 7500 ppm were significantly lower than controls with an increase in liver weight. Histopathology of the livers indicated centrilobular hypertrophy, pericholangitis and a tendency toward bile duct hyperplasia at 7500 ppm. Follicular cell hypertrophy was seen in the thyroid in 3, 5 and 5 rats (N = 5) in 250 through 7500 ppm. The conclusion was that 15 - 18 month old male rats are capable of significant metabolism of carbaryl, and are similar to young rats [see record 209656]. Supplemental study. (Gee, 3/8/04)

169 - 0455 209658 "Carbaryl: Liver cytochrome P-450 inducer phenotyping in the male CD1 mouse." (Thomas, H., Ciba-Geigy Limited, Basel, Report CB 94/23, R013827, October 21, 1994) Livers were from mice treated with 0 or 8000 ppm (1154 mg/kg) in the diet for 14 days (Groups 5 and 4 of record 209659 above under "DNA damage/repair"). Frozen livers were thawed, homogenized and cytosolic and microsomal fractions obtained by centrifugation. The protein content of both fractions was determined. The following parameters were compared: Cytochrome P-450, 7-ethoxyresorufin o-de-ethylase (EROD), 7-pentoxeresorufin o-depentylase (PROD), regio- and stereoselective testosterone hydroxylation and glutathione content. Results: Body weights in treated mice were 85% (28.88) of controls (34.08) and relative liver weights were increased to 135% of controls. Microsomal protein was increased to 132% of controls. Cytochrome P-450 was elevated to 1.3 of control (15.13 nmol/min/g liver* versus 11.21), EROD increased to 1.9 of control, PROD to 3.1, and total testosterone hydroxylation was elevated 152% (86.69* versus 56.95 nmol/min/g liver). The slightly increased level of glutathione did not reach statistical significance. In comparison, carbaryl represented a weak barbiturate-type inducer of cytochrome P-450 system in male mice. Supplemental study. No worksheet. (Gee, 3/4/04)

169 - 402 177759 B. Valles "Carbaryl: Investigation of the metabolism of [14 C]-carbaryl following 14 days administration to the male CD₁ mouse." (Rhone-Poulenc, Sophia Antipolis, Study SA 97481, 6/16/99) Male CD₁ mice (10 per group) were fed diets containing 0, 10, 100, 1000 or 8000 ppm carbaryl for 14 days followed by a single dose of 50 mg/kg [14 C]-carbaryl by gavage on the fifteenth day. Urine and feces were collected at 24-hour intervals following dosing for 168 hours, after which the animals were sacrificed. Radioactivity in the carcass and blood was determined. The metabolites in pooled urine were quantified for 0-24, 24-48 and 48-96 hours. There were 21 components found in the urine with the four major components being the dihydro, dihydroxy-naphthyl sulfate, the hydroxy-carbaryl glucuronide, α -naphthyl sulfate and α -naphthyl β -D glucuronide. The first two, apparently formed by epoxide intermediates, were increased in the mice given 8000 ppm in the diet, suggesting that at high doses of carbaryl, the metabolism, distribution and excretion pattern may be altered with a higher proportion of reactive intermediates being formed. Comparison with results from the rat suggests there are some differences in metabolism, although a more complete study would be required to elucidate the metabolic pathway in mice. Supplemental study. (Gee, 7/8/04)